NOVARTIS

US FOOD & DRUG ADMINISTRATION

ENDOCRINOLOGIC & METABOLIC DRUGS ADVISORY COMMITTEE

Pasireotide (solution for injection) for the treatment of patients with Cushing's disease

Briefing Document

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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List of abbreviations

ACTH	adrenocorticotropic hormone
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
APTT	activated partial thromboplastin time
AUC	area under curve
b.i.d.	twice daily
BCRP	breast cancer resistance protein
BMI	body mass index
BP	blood pressure
BSEP	bile salt export pump
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL/F	apparent total body clearance
CushingQOL	Cushing's disease Health-Related Quality of Life Questionnaire
EMA	European Medicines Agency
DDI	drug-drug interaction
DPP-4	dipeptidyl peptidase-4
DXA	dual-energy X-ray absorptiometry
ECG	electrocardiogram
EOP2	End-of-Phase 2
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FPI	Full Prescribing Information
GEP/NET	gastroenteropancreatic neuroendocrine
GGT	gamma-glutamyltransferase
GH	growth hormone
GIP	glucose-dependent insulinotropic polypeptide
GLP	Good Laboratory Practice
GLP-1	glucagon-like peptide 1
HbA1c	glycosylated hemoglobin
HDL	high density lipoprotein
HRQL	health-related quality of life
ICH	International Conference on Harmonization
IGF-1	insulin-like growth factor 1
INR	international normalized ratio
ITT	Intention to Treat
LDL	low density lipoprotein
LFT	liver function test
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MRP	Multi-drug resistance protein

NDA	New Drug Application
NOAEL	no observed adverse effect level
OATP	organic anion-transporting polypeptide
OCT	organic cation transporter
OGTT	oral glucose tolerance test
PD	pharmacodynamics
P-gp	P-glycoprotein
PK	pharmacokinetics
PT	prothrombin time
QoL	quality of life
QTc	corrected QT interval
RMP	risk management plan
SAE	serious adverse events
s.c.	subcutaneous
SMQ	Standardized MedDRA Query
SOC	system organ class
SPA	Special Protocol Assessment
SSTR	somatostatin receptor
TQT	thorough QT
UGT	uridine diphosphate glucuronosyltransferase
US PI	US Package Insert
UFC	urinary free cortisol
ULN	upper limit of normal
V_2/F	apparent distribution volume

1 Executive summary

1.1 Introduction

Cushing's disease is a very rare, debilitating, and life-threatening disease caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma, which presents with significant morbidities associated with chronic hypercortisolism that have a profound impact on patients' health and quality of life. The current first-line treatment for patients with Cushing's disease is transphenoidal resection of the adenoma. For patients with persistent/recurrent Cushing's disease following surgery, or for whom surgery is not an option, therapeutic alternatives are very limited.

Pasireotide is a second-generation somatostatin analog. It has a broader somatostatin receptor (SSTR) binding profile than currently available somatostatin analogs, which are not effective in treating Cushing's disease. The high affinity of pasireotide to SSTR5, which is expressed at high levels in ACTH-secreting tumors in Cushing's disease, underlies the rationale for developing pasireotide in Cushing's disease.

Pasireotide has been developed as an immediate release formulation for subcutaneous (s.c.) injection and as a long-acting release (LAR) formulation for intramuscular injection. The s.c. formulation has been extensively investigated both in healthy volunteers and patient studies. Novartis is seeking approval for pasireotide injection for s.c. use for treatment of patients with Cushing's disease who require medical therapy. The New Drug Application (NDA 200677) was submitted to the Food and Drug Administration (FDA) on 17-Feb-2012.

NDA 200677 was primarily based on data from the 12-month core phase of the Phase III study B2305. Results from the Phase II study B2208 provided proof-of-concept for the treatment of patients with Cushing's disease. Long-term extensions of B2305 and B2208E provide additional long-term safety and efficacy data for the use of pasireotide in the treatment of patients with Cushing's disease. In addition, safety data for pasireotide s.c. in other indications and from studies in healthy volunteers were included in the NDA. These comprise 2 studies in patients with acromegaly (B2103 and B2201 with extension B2201E), one study in carcinoid syndrome (B2202), 7 studies in healthy volunteers, and 5 special safety studies. Taken together, the results of these studies provide compelling evidence for a positive benefit-risk profile of pasireotide in patients with Cushing's disease, a patient population with limited therapeutic options available.

The European Commission granted marketing approval in the EU for pasireotide (Signifor®) in Cushing's disease on 24-April-2012, with a starting dose of 600 µg b.i.d. s.c. with option of dose increase to 900 µg b.i.d. and decrease to 300 µg b.i.d.

This Briefing Document provides background information on the clinical development program for pasireotide and summarizes nonclinical and clinical information included in the NDA.

1.2 Cushing's disease

1.2.1 Pathophysiology and epidemiology

Cushing's disease is caused by an ACTH-secreting pituitary adenoma. The elevated levels of ACTH stimulate the adrenal glands to produce excess cortisol, thereby leading to the subsequent development of the clinical signs and symptoms of hypercortisolism (also known as Cushing's syndrome).

Epidemiological data on Cushing's disease are scarce, and only limited information is available for the US. The annual incidence of Cushing's disease ranges from 1.2 to 2.4 per million in Europe, with a prevalence of 0.39 to 0.56 per 10,000. The incidence in women is 3-8 times higher than in men. Using the prevalence estimates from published studies, about 40,000 patients are projected to be living with Cushing's disease in the USA, Japan and EU (USA ~16,848, Japan ~6,604, EU ~16,120; Daly et al 2006, Ambrosi et al 1991, Etxabe and Vazquez 1994, Davis et al 2001, Lindholm et al 2001, Fernandez et al 2012).

Chronic hypercortisolism leads to significant morbidity and increased mortality. The majority of patients are obese or overweight with characteristic central obesity and facial fullness. Hypertension, impaired glucose tolerance/diabetes and dyslipidemia are also common. Changes in physical appearance include hirsutism, thinning of skin with easy bruising and purplish striae. Hypercortisolism is also associated with muscular atrophy, generalized weakness and fatigue, osteopenia/osteoporosis, gonadal dysfunction, and immune deficiency with an increased risk for infections. Chronic hypercortisolism has significant impact on patients' quality of life, with many patients suffering from depression, emotional instability, sleep disorders, and problems with personal relationships and school or work performance. The mortality rate is 4 times higher than age- and gender-matched subjects if not treated, mainly due to cardiovascular complications (Arnaldi et al 2003, Pivonello et al 2008, Webb et al 2008, Deckers et al 2007, Clayton et al 2010).

1.2.2 Treatment landscape

Pituitary surgery is the first-line therapy for Cushing's disease. Remission rates following initial surgery are 70–90% in patients with microadenomas and 50–65% in patients with macroadenomas in the hands of experienced neurosurgeons. Recurrence occurs in 10-30% of patients, mostly within 5 years of surgery, however recurrence may occur a decade or more after successful surgery. There is no consensus on treatment for patients in whom surgery failed or surgery is not feasible (Biller et al 2008). Repeat pituitary surgery is an option; however, success rates are lower (30-50%) and carry a higher risk of pituitary insufficiency. Remaining non-medical treatment options are irradiation of the pituitary or bilateral adrenalectomy, however both options are associated with significant sides effects (Biller et al 2008, Pivonello et al 2008, Blevins et al 2009).

To date, long-term data in the treatment of Cushing's disease with pharmacological agents has been limited. Drugs targeting the adrenal glands (steroidogenesis), and more recently, the pituitary, have been available for many years and have been tested in smaller studies (Biller et al 2008). Compounds most frequently used worldwide (such as ketoconazole and metyrapone) are generally not indicated for the treatment of Cushing's disease and have not been tested in prospective, randomized clinical trials. Recently, the glucocorticoid receptor blocker

mifepristone (Korlym) was approved by the FDA for the treatment of hyperglycemia in patients with Cushing's syndrome with impaired glucose tolerance or diabetes mellitus. There is, however, no consensus on the medical management of Cushing's disease and many patients cannot be controlled effectively in the longer term. There are no approved pituitary tumor-directed and cortisol-reducing treatment options available for patients with persistent, recurrent Cushing's disease or patients who are not surgical candidates and require medical intervention.

It is apparent that there is an unmet medical need for a treatment that will act directly on the pituitary tumor to normalize ACTH and cortisol levels, control tumor growth, reverse co-morbidities, and improve quality of life and overall survival.

1.3 Pasireotide

Pasireotide is a second-generation analog of the natural peptide hormone somatostatin. Somatostatin and SSTRs are widely distributed in the human body and are important regulators of endocrine and exocrine secretion, affecting the regulation of many hormones such as growth hormone (GH), glucagon, insulin, gastrin, secretin, and thyroid-stimulating hormone (Reichlin 1983). In comparison to the already available analogs of somatostatin, pasireotide has a broader receptor binding profile, displaying binding affinity and functional activity for 4 of the 5 SSTR subtypes (Schmid and Schoeffter 2004).

In vitro studies have shown that corticotroph (ACTH-releasing) tumor cells from patients with Cushing's disease express high levels of SSTR5, whereas the other receptor subtypes are not expressed or expressed at a significantly lower level. As the affinity of pasireotide for SSTR5 is high, it was postulated that it would be effective in the treatment of Cushing's disease by inhibiting the release of ACTH and consequently decreasing adrenal corticosteroid production. This mechanistic rationale was supported by preclinical studies showing that pasireotide inhibits ACTH secretion in vitro and in vivo with greater efficacy than octreotide. The clinical development program in patients with Cushing's disease also supported the efficacy of pasireotide as a pituitary-directed treatment.

1.3.1 Non-clinical development

The nonclinical profile of pasireotide has been characterized in a comprehensive testing program that included in vitro studies and in vivo studies in mice, rats, rabbits and monkeys. These studies include pharmacology studies, non-clinical absorption, distribution, metabolism, excretion (ADME) studies, and toxicology studies (acute, subchronic and chronic toxicity studies, carcinogenicity studies in transgenic mice, local tolerance studies, reproduction studies, as well as in vitro and in vivo genotoxicity studies). Most of these studies were performed using the s.c. route of administration.

Pasireotide had no relevant adverse effects on vital organ functions. It is not genotoxic and showed no carcinogenic effects. Reproductive toxicity studies demonstrated no teratogenic effects, and no adverse effects on male fertility. Reduced female fertility and slower postnatal development are observed, and are likely results of pharmacological effects. The vast majority of the findings in toxicology studies, including effects on pituitary gland, reduced hematopoietic activity in the hematopoietic organs, and prolongation of the estrus cycle in

rats, and effects on pituitary, thyroid, large intestine and injection sites in the monkey, are considered related to the pharmacology of pasireotide.

1.3.2 Clinical pharmacology

An extensive clinical pharmacology program has been performed with pasireotide s.c. in healthy volunteers and patients with Cushing's disease. The results show that pasireotide is rapidly absorbed, with a large volume of distribution, and low clearance, both in healthy volunteers and patients with Cushing's disease. The effective half-life is approximately 12 hours in healthy volunteers. Pasireotide is primarily eliminated via biliary excretion into feces as unchanged drug.

Pasireotide exposure is dose-proportional in patients with Cushing's disease. Dose adjustment is recommended for patients with moderate hepatic impairment, whereas patients with severe hepatic impairment should not be treated with pasireotide s.c. No dose adjustment is required for age, body weight, mild hepatic impairment, or renal impairment.

At therapeutic dose levels, the potential of protein binding, metabolism and/or transporter mediated drug-drug interaction (DDI) between pasireotide and co-medications is low.

The PK/PD relationship between pasireotide exposures and UFC levels has been assessed by two different approaches in study B2305.

- A logistic regression based on pasireotide through concentrations and UFC response from all patients at Month 3 showed a flat relationship between pasireotide exposure and probability of UFC normalization.
- When looking into sub-groups of patients by response status, an E_{max} model analysis based on data from patients with UFC response at Month 6 collected over 12 months suggests a trend that increases in pasireotide trough concentrations are associated with lower UFC levels. However, because of high inter-patient variability in trough concentrations, there is significant overlap of the exposures achieved for the two doses.

Taken together, the results indicate that the probability of achieving normalization of UFC is comparable for the 600 µg b.i.d. and 900 µg b.i.d. doses.

1.3.3 Clinical studies in Cushing's disease

The efficacy of pasireotide s.c. in Cushing's disease is primarily derived from the 12-month core phase of the Phase III study B2305. In addition, results from the Phase II study B2208 provide proof-of-concept, and the long-term extensions of B2305 and B2208E provide additional long-term safety and efficacy data in patients with Cushing's disease.

1.3.3.1 Study B2305

Study B2305 was a randomized, double-blind Phase III study that evaluated safety and efficacy of 2 doses of pasireotide s.c. in 162 patients with persistent/recurrent Cushing's disease post-pituitary resection or de novo Cushing's disease who were not candidates for surgery. This is the largest prospective study conducted to date in patients with Cushing's disease. Patients had to have confirmed diagnosis of Cushing's disease and baseline UFC at least 1.5 times the upper limit of normal (ULN) of 145 nmol/24h. Given the morbidity

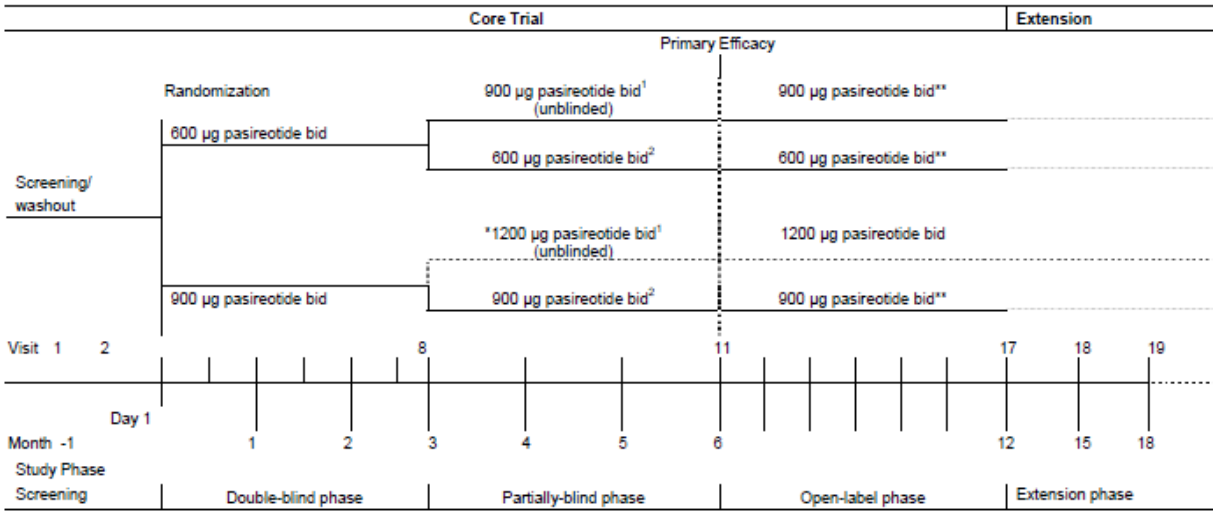
associated with chronic hypercortisolism, the study did not include a placebo arm due to ethical considerations.

Patients were randomized 1:1 to receive pasireotide 600 µg b.i.d. or 900 µg b.i.d. At Month 3, patients continued at this dose until Month 6 (double-blind treatment) if their Month 3 UFC was ≤ 2xULN and ≤ baseline UFC. Patients not meeting these criteria at Month 3 were to be unblinded and their dose increased by 300 µg b.i.d.; those whose dose was not increased had to be discontinued from the study.

After 6 months, patients entered an open-label treatment period where they remained on their current dose level provided a response was observed. If the patient did not respond, or the response was not maintained during the open-label treatment period, the dose could be increased by 300 µg b.i.d. to a maximum daily dose of 1200 µg b.i.d. Dose decrease by 300 µg b.i.d. was allowed any time for lack of tolerability.

The duration of the core study was 12 months, after which patients could enter an open-ended extension, allowing further assessment of long-term efficacy and safety.

Design of Phase III study B2305 in patients with Cushing's disease



[1] Patients with baseline UFC ≥ 2xULN and Month 3 UFC >2xULN or baseline UFC < 2xULN and Month 3 UFC > baseline UFC

[2] Patients with baseline UFC ≥ 2xULN and Month 3 UFC ≤ 2xULN or baseline UFC < 2xULN and Month 3 UFC ≤ baseline UFC

* Permitted dose increase if patient had tolerated 900 µg b.i.d.

** During open-label phase dose could be increased by 300 µg at any time if response was lost

All doses could be reduced by 300 µg at any time for tolerability

China only: doses higher than 900 µg b.i.d. were not allowed

1.3.3.2 Study B2208 and its extension B2208E

Study B2208 was a multicenter, open-label, single-arm, proof-of-concept study to assess the safety and efficacy of pasireotide 600 µg b.i.d. s.c. in 39 adult patients with de novo or recurrent Cushing's disease post-pituitary resection. The duration of the study was 15 days. The primary efficacy endpoint was the normalization of UFC levels after 15 days of treatment. The study enrolled 39 patients, of which 10 were excluded from the primary

efficacy evaluation because they had either baseline UFC within normal range, or less than 2 UFC samples at baseline or end-of-study.

Study B2208E was an open-ended extension to B2208 for which patients who completed the core study and who benefited from treatment could enroll. Dose escalation up to a maximum dose of 900 µg b.i.d. was permitted. Nineteen patients continued pasireotide treatment in the extension.

1.4 Overview of efficacy of pasireotide in Cushing's disease

1.4.1 Efficacy endpoints in B2305

The primary efficacy endpoint in B2305 was the proportion of responders, i.e. patients with UFC ≤ ULN at Month 6. To avoid a potential confounding by dose increases, patients who had dose-escalation prior to Month 6 were considered non-responders in this analysis, regardless of their UFC levels at Month 6. Missing Month 6 UFC values were imputed by the last available value between Month 3 and Month 6.

Evaluation of the primary efficacy endpoint at Month 6 was chosen in agreement with the FDA as adequate for the efficacy evaluation of a compound intended for chronic treatment. Sustainability of response was evaluated by inclusion of an additional treatment period of 6 months, bringing the total duration of the core study to 12 months.

The proportion of responders in each dose group was summarized using the point estimate and the 2-sided 95% CIs. If the lower bound of the 95% CI for a dose group was greater than 15% then that dose group was considered to have a significant benefit in terms of UFC reduction. The response rate of 15% was considered to provide significant benefit in terms of UFC reduction in this setting, given the lack of medications that can be used long-term with demonstrated efficacy and safety, and the fact that UFC rarely normalizes spontaneously in patients with Cushing's disease (for further discussion see Section 3).

To support the primary analysis, additional **clinical response subgroups** were defined as follows:

- **Controlled:** Month 6 UFC ≤ ULN (regardless of dose increase).
- **Partially controlled:** Month 6 UFC > ULN but UFC decreased by at least 50% from baseline (regardless of dose increase).
- **Uncontrolled:** neither controlled nor partially controlled at Month 6**.**

Secondary efficacy analyses included proportion of patients with response defined as UFC ≤ ULN at time points up to Month 12, changes in plasma ACTH, serum and salivary cortisol levels, clinical signs and symptoms of Cushing's disease, tumor volume as measured by magnetic resonance imaging (MRI), Cushing's disease-specific health-related quality of life (HRQL) as measured by a Cushing's Disease Health-Related Quality of Life Questionnaire (CushingQOL), and the Beck depression inventory score.

1.4.2 Demographics and patient disposition in B2305

Study B2305 enrolled 162 patients with Cushing's disease at 68 sites in 18 countries, with 25 patients enrolled in the USA and Canada. Patient demographics were as expected in a

population with Cushing's disease. Patients had a mean age of approximately 40 years, with fewer than 5% overall aged 65 or over. Women accounted for three quarters of all patients.

The majority of patients had moderate to severe hypercortisolism at baseline. The overall mean UFC (970 nmol/24hr) was several times above the ULN of 145 nmol/24h; 84% of patients had UFC >2xULN, and 38% had UFC >5xULN. Furthermore, baseline mean UFC levels were higher in the 600 µg b.i.d. group than in the 900 µg b.i.d. group (mean±SD: 1155.9 ± 2629.78 and 781.2 ± 926.38 nmol/24h, respectively).

With the exception of baseline UFC, other patient characteristics were similar for both dose groups. Consistent with the severity of disease are the observations that patients on average had high blood pressure (BP; mean 133.5/86.3 mmHg, were obese (mean BMI 30.3 kg/m^2, mean waist circumference 103.1 cm), and had elevated total cholesterol (mean 5.8 mmol/L).

Of the 162 randomized and treated patients, 107 (66.0%) completed the Month 6 assessment (primary efficacy analysis) and 78 (48.1%) completed Month 12 (end of core). Fifty-eight patients entered the optional extension, and 20 chose not to continue.

97 patients (59.9%) discontinued the study (core or extension) at any time up to data cut-off. The most frequent reason for discontinuation was unsatisfactory therapeutic effect (25.3% of patients), followed by adverse event (AE; 17.3%) and withdrawal of consent (14.8%). The rates of discontinuation, and the reasons for discontinuation, were similar in both dose groups.

1.4.3 Efficacy results in B2305

Primary efficacy results are shown in Table 1-1. Consistent and meaningful reductions in UFC were seen in both dose groups. The 900 µg b.i.d. dose group met the primary efficacy endpoint, with a response rate of 26.3% at 6 months (95% CI 16.6 to 35.9; the lower bound of the 95% CI was greater than the pre-specified null hypothesis of 15%). The 600 µg b.i.d. group did not meet the primary efficacy endpoint as the response rate was 14.6% (95% CI 7.0 to 22.3).

Note that due to the higher baseline mean UFC, the 600 µg b.i.d. group was intrinsically less likely to meet the primary efficacy endpoint. However, the relative decrease in UFC levels in both dose groups was comparable and clinically relevant, as discussed in the sections below.

Table 1-1 Primary efficacy analysis – number of responders at Month 6 (B2305)

	Pasireotide 600 µg b.i.d. N=82	Pasireotide 900 µg b.i.d. N=80	Overall N=162
Response - n (%)	12 (14.6)	21 (26.3)	33 (20.4)
95% Confidence Interval	(7.0, 22.3)	(16.6, 35.9)	(14.2, 26.6)

95% Confidence Intervals are based on normal approximation to the binomial distribution.

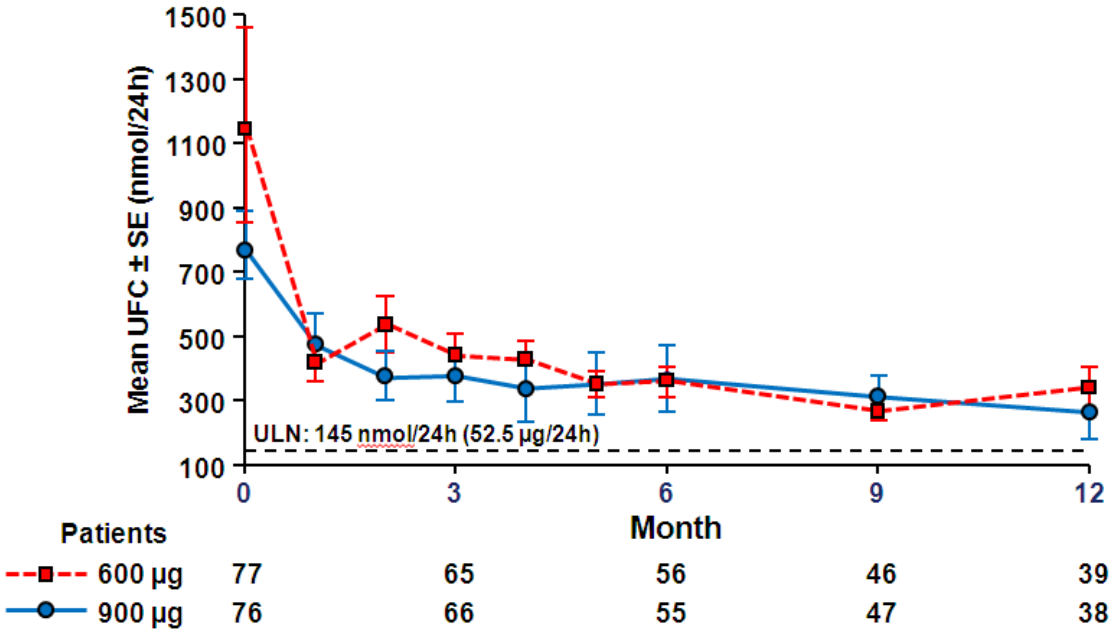
Missing Month 6 values were imputed for 2 patients in each group.

Three patients (1 in the 600 µg b.i.d. and 2 in the 900 µg b.i.d. groups) were considered non-responders because they had a dose increase prior to Month 6.

As shown in Figure 1-1, there was a robust decrease in UFC levels in both dose groups within the first month of treatment. At Month 6, the mean absolute change from baseline was -463.4 and -364.9 nmol/24h for the 600 and 900 µg b.i.d. groups, respectively. Note that the median

% decrease in UFC was similar in both dose groups (both 47.9%). In both dose groups mean UFC levels decreased to comparable levels at Month 6 and remained stable thereafter.

Figure 1-1 UFC levels up to Month 12 (B2305)



A minimum of 3 UFC samples were required at Months 0 (baseline), 3, 6 and 12, and a minimum of 2 UFC samples were required at other time points; otherwise a patient's UFC assessment at that time point was considered missing.

Supportive analyses for the primary endpoint showed that at Month 6, the proportion of patients with controlled UFC (i.e. UFC ≤ ULN regardless of prior dose increase) was 15.9% and 28.8% in the 600 and 900 µg b.i.d. groups, respectively (Table 1-2). The proportion of patients with partial control (i.e. UFC above ULN but at least 50% decreased from baseline) was 18.3% in the 600 µg b.i.d. group and 12.5% in the 900 µg b.i.d. group. Taken together, the proportion of patients who were at least partially controlled at Month 6 was 34.1% and 41.3% in the 600 and 900 µg b.i.d. groups, respectively.

Table 1-2 Clinical response subgroups at Month 6 and Month 12 (B2305)

	Month 6		Month 12	
	Pasireotide 600 µg b.i.d. N=82	**Pasireotide 900 µg b.i.d. N=80**	**Pasireotide 600 µg b.i.d. N=82**	**Pasireotide 900 µg b.i.d. N=80**
Controlled or partially controlled – n (%)	**28 (34.1)**	**33 (41.3)**	**24 (29.3)**	**22 (27.5)**
Controlled – n (%)	13 (15.9)	23 (28.8)	11 (13.4)	20 (25.0)
Partially controlled – n (%)	15 (18.3)	10 (12.5)	13 (15.9)	2 (2.5)

Controlled responders: UFC ≤ ULN (regardless of dose increase).

Partially controlled responders: UFC >ULN but had at least 50% decrease from baseline, regardless of dose increase.

Missing Month 6 UFC was imputed for a total of 8 patients (2 controlled patients in each dose group and 2 partially controlled patients in each dose group).

Prior to Month 6, the pasireotide dose was increased in 36 patients (24 and 12 patients in the 600 and 900 µg b.i.d. groups, respectively). At Month 6, 1 patient with a dose increase from 600 µg b.i.d. to 900 µg b.i.d. and 2 patients with a dose increase from 900 µg b.i.d. to 1200 µg b.i.d. achieved control. Among patients with partial control at Month 6, 8 of 15 patients in the 600 µg b.i.d. group and 1 of 10 patients in the 900 µg b.i.d. group had a dose increase prior to Month 6.

In addition to suppression of UFC, clinically relevant decreases in plasma ACTH and serum cortisol levels were seen in both dose groups. Furthermore, clinically relevant shrinkage of pituitary tumor volume was observed in the 900 µg b.i.d. group among patients with measurable tumor volume at baseline. The suppression of ACTH and the shrinkage of pituitary tumor volume are particularly important as they support the proposed pituitary-targeted mechanism of action of pasireotide.

As expected in a patient population with moderate-to-severe hypercortisolism, patients in B2305 were on average overweight or obese, hypertensive, and had elevated cholesterol levels. Pasireotide treatment resulted in clinically relevant improvements in BP, body weight, and lipids (total cholesterol, LDL and triglycerides) in both treatment groups. At Month 6, the mean decrease in BP was 6.8/4.2 mmHg in the 600 µg b.i.d. group, and 11.4/5.0 mmHg in the 900 µg b.i.d. group; the decrease was more pronounced with longer follow up, and it should be noted that BP decreased primarily in hypertensive but not in normotensive patients. Clinically relevant and sustained improvements were also seen with both pasireotide doses for weight, BMI, waist circumference as well as lipids (total cholesterol, LDL and triglycerides, with little change in HDL. In addition, improvements in features such as facial rubor, striae, and bruising were also noted in both dose groups. The improvements were more pronounced in patients whose UFC was controlled at Month 6, regardless of dose group, however improvements were also seen in patients whose UFC did not normalize.

HRQL, measured by the disease-specific CushingQOL instrument, improved with pasireotide treatment in both dose groups. Importantly, improvements in clinical signs and symptoms as well as CushingQOL were sustained up to 12 months and were observed in patients experiencing reductions in UFC even if complete normalization did not occur.

The results of the extension with a data cut-off at Month 33 showed that UFC levels remained suppressed with continued pasireotide treatment. The improvements in clinical manifestations of hypercortisolism (notably BP and weight) seen during the core phase were sustained for patients who remained on treatment.

1.4.4 Efficacy results in B2208

In B2208, patients with de novo, persistent or recurrent Cushing's disease were treated with pasireotide 600 µg b.i.d. for 15 days. In this short-term study, UFC normalized in 5 out of 29 patients (17%), and 22 patients (76%) experienced a decrease in UFC. Mean UFC level decreased from 1231 nmol/24 h at baseline to 683 nmol/24 h at day 15 (a reduction of 44.5%).

Decreases in mean serum cortisol and plasma ACTH were also demonstrated. A slight decrease in BP was seen in most patients in the core study in spite of the short treatment duration (15 days).

In the long-term extension B2208E, UFC normalized in 4 out of 18 patients after 6 months of treatment, In addition, a consistent reduction in mean UFC relative to core baseline values was maintained throughout the extension study period. A beneficial effect on diastolic BP was also evident.

1.5 Overview of safety of pasireotide

1.5.1 Safety population

The safety review for pasireotide s.c. in patients in Cushing's disease focuses on the results from Phase III study B2305 with 162 patients in the safety population; 82 patients randomized to the 600 µg b.i.d. and 80 patients randomized to 900 µg b.i.d.

The total safety population, including patients/healthy volunteers who received at least one dose of pasireotide, comprises a total of 726 subjects. This included 201 patients with Cushing's disease (B2305 and B2208/E), 72 patients with acromegaly (B2103 and B2201/E, and 45 patients with carcinoid syndrome (B2202). In special safety studies there were 127 pasireotide-treated healthy volunteers in the QT/QTc profile study B2113, 34 subjects (15 healthy volunteers and 19 patients with hepatic impairment) in the hepatic impairment study B2114, 90 healthy male volunteers in the glucose metabolism study B2124, 112 healthy male and female volunteers in a TQT study B2125, and 45 healthy male volunteers in an investigator-led glucose metabolism study B2216.

1.5.2 Safety conclusions

The safety profile of pasireotide in patients with Cushing's disease is consistent with that of other somatostatin analogs, with the exception of an increased incidence and severity of hyperglycemia. The results from studies B2305 and B2208 (including patients treated long-term in the extension) are consistent with the known class effects. Gastrointestinal disturbances were frequently observed, but most cases were transient, mild in severity and did not require additional therapy or treatment interruption. Cholelithiasis, a known class effect of somatostatin analogs, was also observed in patients with Cushing's disease, however most patients were asymptomatic and did not require discontinuation of treatment.

Hyperglycemia represents the main adverse event with pasireotide therapy. Dysregulation of glucose metabolism is common in patients with Cushing's disease, and this was reflected in a high proportion of patients in B2305 who were pre-diabetic or diabetic at baseline. In B2305, AEs linked to hyperglycemia were reported in around 70% of patients, with a higher incidence seen for patients characterized as diabetic at baseline. Furthermore, grade 3-4 hyperglycemia-related AEs and serious adverse events (SAEs) were most frequent among diabetic patients, and in particular those in the 900 µg b.i.d. group, where around half of all patients had a grade 3 event. Grade 3-4 hyperglycemia-related events were infrequent in patients with normal glucose tolerance at baseline, regardless of dose group.

Fasting plasma glucose (FPG) levels peaked within the first month of treatment, with higher increases seen in patients who were diabetic at baseline (in particular those randomized to 900 µg b.i.d.). FPG levels then decrease and stabilized, with factors such as decreases in circulating cortisol, attenuation of effect over time, decreases in weight, decreases in insulin resistance, and anti-diabetic intervention playing a role. Glycosylated hemoglobin (HbA1c)

levels increased and stabilized by Month 2 in both dose groups, with higher increases seen in pre-diabetic and diabetic patients. Pasireotide-induced hyperglycemia was rapidly reversible upon discontinuation of treatment, with FPG levels decreasing to near-baseline levels within 1 month after last administration of pasireotide.

Recent mechanistic studies in healthy volunteers have clarified that the underlying mechanism is related to inhibition of insulin and incretin secretion without changes in insulin sensitivity, and that, besides insulin, incretin-based therapies are the most promising class of agents for managing the hyperglycemia. A study is being initiated to confirm this in patients with Cushing's disease. Furthermore, exposure-response analysis showed a greater probability for 900 µg b.i.d. to increase HbA1c by >1% than 600 µg b.i.d. Considering these recent advances in understanding the effect of pasireotide on glucose metabolism, hyperglycemia in patients with Cushing's disease receiving pasireotide treatment should be manageable.

Mild, transient elevations in liver function tests (LFTs) were seen in patients and healthy volunteer studies across the pasireotide s.c. development program. Elevations resolved spontaneously while on pasireotide or following treatment discontinuation and were without clinical sequelae. Three cases (0.6%) of alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >3xULN and total bilirubin ≥2xULN were identified in healthy volunteer studies. In addition, a patient with Cushing's disease in a compassionate use program had concomitant elevations of ALT >10xULN and total bilirubin ≥2xULN. The 3 healthy volunteer cases did not present with the classic clinical picture of severe hepatocellular damage, whereas for the patient with Cushing's disease follow-up information revealed a clinical picture most consistent with hepatitis. There were no patients with concomitant elevations of ALT/AST >3xULN and total bilirubin ≥ 2xULN across all Phase II and III clinical studies in the pasireotide clinical program.

The results of 2 thorough QT (TQT) studies of pasireotide in healthy volunteers indicated a mild QT-prolonging effect. The maximal placebo-corrected QTcI prolongation with the supra-therapeutic dose of 1950 µg b.i.d. was 16.12 ms, and the dose-response relationship between 600 µg b.i.d. and 1950 µg b.i.d. was relatively flat. Pre-clinical data did not indicate a potential for pasireotide to prolong cardiac conduction intervals. The incidence of AEs indicative of arrhythmogenic potential (e.g. QT prolongation, syncope) across the pasireotide s.c. program was 0.6% (4/617) in healthy volunteers and 5.3% (17/318) in patients. No episodes of torsade de pointes have been observed. The number of healthy volunteers and patients with notable post-baseline QTcF interval values (QTcF>480ms or QTcF>500 ms or QTcF change from baseline >60 ms) was low (11/829, 1.3%). Overall, episodes of QT prolongation were mostly sporadic and of single occurrence with no clinical consequence suggestive of an arrhythmogenic potential.

Hypocortisolism (or cortisol withdrawal syndrome) is an expected consequence of effective treatment for Cushing's disease. AEs indicative of hypocortisolism (i.e. clinical symptoms consistent with adrenocortical insufficiency or glucocorticoid withdrawal) were reported in 13 (8%) patients in study B2305. Such events can be managed by appropriate dose adjustments of pasireotide or short-term exogenous glucocorticoid replacement.

Long-term follow-up data with an additional 21 months of follow-up in B2305, and 30 months for B2208E, did not reveal any new safety concerns, and showed that pasireotide was well tolerated in patients with Cushing's disease.

1.6 Recommendation of starting dose

The recommended initial dose of pasireotide is 600 µg b.i.d. by s.c. injection, with optional dose increase to 900 µg b.i.d. In Study B2305, the 900 µg b.i.d. dose group met the primary efficacy endpoint while the 600 µg b.i.d. dose group did not. However, it is important to note that baseline mean UFC levels were higher in the 600 µg b.i.d. group than the 900 µg b.i.d. group. Nevertheless, both dose groups achieved marked reductions in UFC that were sustained over time, and that are considered clinically meaningful not only for patients achieving normal UFC levels. The reductions in UFC were also associated with similar improvements in signs and symptoms such as BP, LDL, body weight and CushingQOL in both dose groups.

After adjusting for baseline UFC, an analysis of the relationship between trough concentrations and the probability of UFC normalization showed that the efficacy of 600 µg b.i.d. was comparable to that of 900 µg b.i.d., while a similar analysis showed a greater probability for 900 µg b.i.d. to increase HbA1c by >1% than 600 µg b.i.d.

Based on the above considerations, a starting dose of 600 µg b.i.d. with optional dose increase to 900 µg b.i.d. provides a better benefit-risk profile than a starting dose of 900 µg b.i.d.

1.7 Benefit/risk assessment

Patients with Cushing's disease have high morbidity and mortality rates and a significantly reduced quality of life. The complex morbidity resulting from chronic hypercortisolism is sometimes difficult to manage and there are currently no approved pituitary-directed pharmacological therapies available for treatment.

Pasireotide is the first medical therapy to demonstrate efficacy by directly addressing the underlying mechanism of Cushing's disease by suppressing ACTH secretion, with associated clinically relevant decreases in cortisol levels measured in serum, saliva and urine. Reductions in ACTH and cortisol levels were rapid, robust and sustained with longer follow-up (>2 years). Pasireotide therapy also resulted in shrinkage of pituitary tumor volume in a relevant subset of patients with measurable tumor volume. Additionally, clinically relevant improvements in signs and symptoms of hypercortisolism, such as BP, weight, BMI and cholesterol levels, were observed even in patients without complete normalization of UFC. Patients also experienced improvement in quality of life related to Cushing's disease, as measured by the Cushing's disease-specific CushingQOL instrument. Overall, clinically meaningful improvements in both biochemical measures of Cushing's disease and signs and symptoms of hypercortisolism have been observed. These represent clear benefits associated with treatment with pasireotide.

The safety profile of pasireotide is comparable to that of other somatostatin analogs, with the exception of a higher incidence and degree of hyperglycemia. The underlying mechanism of pasireotide-associated hyperglycemia is now well understood. It has been shown to be secondary to inhibition of insulin and incretin secretion without changes in insulin sensitivity, and is rapidly reversible upon discontinuation of treatment. Results of mechanistic studies in healthy volunteers suggest that pasireotide-associated hyperglycemia responds to anti-diabetic treatment, such as DPP-IV inhibitors, GLP-1 analogues/mimetics or insulin.

Patients with Cushing's disease, who are not successfully treated with surgery, have limited options. Persistent or recurrent hypercortisolism can lead to severe morbidity and ultimately mortality. Overall, pasireotide has a favorable benefit/risk profile in patients with persistent/recurrent Cushing's disease, providing patients with improvement in both cortisol levels and other signs and symptoms of their disease in the context of a well understood safety profile. The results show that pasireotide is effective, and can be safely used with appropriate management.

2 Introduction

2.1 Indication

Novartis is seeking approval for pasireotide s.c. as a somatostatin analog indicated for the treatment of patients with Cushing's disease who require medical therapeutic intervention.

Pasireotide was developed as a second-generation SSTR ligand with a broader binding profile compared with the first-generation somatostatin analogs octreotide and lanreotide, including high affinity to SSTR5. In Cushing's disease, patients have an ACTH-secreting pituitary tumor, which results in excessive cortisol production by the adrenal glands and the resulting Cushing's syndrome. These pituitary tumors have high expression of SSTR5. By binding to SSTR5 in the corticotroph tumors, pasireotide is a targeted therapy which reduces the secretion of ACTH from the tumor, leading to decreasing and even normalization of cortisol levels and to amelioration of the signs and symptoms associated with hypercortisolism.

2.2 Cushing's disease

2.2.1 Pathophysiology

Cushing's disease is a very rare, debilitating, and life-threatening disease caused by an ACTH-secreting pituitary adenoma. The tumors are usually microadenomas (≤ 1 cm in diameter); macroadenomas are rare (Orth 1995). The elevated levels of ACTH secreted by these tumors stimulate the adrenal glands to produce excess cortisol, thereby leading to the subsequent development of the clinical signs and symptoms of hypercortisolism. The normal circadian rhythm of cortisol production is usually lost. In patients with Cushing's disease, most adenomatous cells develop a high set-point for feedback inhibition of ACTH secretion by cortisol, which may lead to loss of tumor differentiation to the point where increased cortisol levels can no longer suppress ACTH production and release. Cushing's disease is the most common form (around 80% of cases) of endogenous Cushing's syndrome, which is a constellation of signs and symptoms that result from excess circulating levels of cortisol (Boscaro et al 2001, Biller et al 2008).

Most patients are obese or overweight, with abdominal visceral adiposity and facial fullness (moon face). More than 70% have hypertension, around 80% have impaired glucose tolerance or diabetes (often due to insulin resistance), and dyslipidemia is seen in around 20% of patients. Changes in physical appearance commonly include hirsutism, thinning of skin with easy bruising, purplish striae, reddening of the cheeks, and ulceration of the skin. Hypercortisolism is also associated with muscular atrophy, generalized weakness and fatigue, osteopenia/osteoporosis, menstrual disorders in women, decreased fertility and/or libido, and

immune deficiency with an increased risk for infections. The physiological and physical changes resulting from chronic hypercortisolism have significant impact on patients' quality of life, with many patients suffering from depression, emotional instability, sleeping difficulties; 80% of patients report interference with family life and relations with their partner, and more than half with school of work performance (Arnaldi et al 2003, Pivonello et al 2008, Webb et al 2008, Feelders et al 2012).

Patients with untreated Cushing's disease have a mortality rate 4 times higher than age- and gender-matched subjects which is mainly caused by cardiovascular complications. As described above, hypercortisolism is characterized by a series of systemic complications, including abdominal obesity, systemic arterial hypertension, and impairment of glucose tolerance, dyslipidemia, and hypercoagulability, which increase cardiovascular risk. Cardiovascular complications associated with hypercortisolism such as coronary artery disease, congestive heart failure and stroke significantly increase the mortality rate of these patients compared with the normal population (Pivonello et al 2005, Arnaldi et al 2003, Pivonello et al 2008, Hammer et al 2004). Dekkers et al (2007) reported that the most frequent causes of death were cardiovascular disease (23.4%), cerebrovascular disease (12.8%), malignancy (19%), and infectious diseases (17%).

In general, patients suffer from the disease for many years before seeking medical attention. Moreover, appropriate diagnosis may be delayed due to lack of awareness of the disease by general practitioners, and the complexity of the diagnosis of the disease due to the non-specificity of the clinical manifestations and the variability in ACTH and cortisol levels.

2.2.2 Epidemiology

Epidemiological data on Cushing's disease are scarce, and only limited information is available for the US. The annual incidence of Cushing’s disease in available studies ranges from 1.2 to 2.4 per million in Europe, with a prevalence of 0.39 to 0.56 per 10,000 (Ambrosi et al 1991, Etxabe and Vazquez 1994, Davis et al 2001, Lindholm et al 2001, Fernandez et al 2012). Using the prevalence estimates from published studies, it can be projected that currently there are about 40,000 patients living with Cushing’s disease: United States (~16,848), Japan (~6,604), France, Germany, Italy, Spain and the United Kingdom (~16,120 in the EU) combined (based on information provided in Daly et al 2006). The disease is 3 to 8 times more frequent in women than men (Boscaro et al 2001). It is diagnosed usually between 25 to 45 years of age (Orth et al 1992).

2.2.3 Diagnosis of Cushing's disease

The diagnosis of Cushing’s disease is complicated by the non-specificity and high prevalence of common signs and symptoms (obesity, hypertension and depression) in patients without the disorder. Furthermore, the clinical manifestations depend on both the degree and the duration of hypercortisolism. Because of this complexity a sequential approach to diagnosis is required. The first step is to confirm the diagnosis of endogenous Cushing’s syndrome (CS); a pathologic hypersecretion of cortisol (including the exclusion of pseudo Cushing’s). The second step is to determine if the CS is ACTH-dependent or independent. The third step is to determine the source of hypersecretion of ACTH in patients with ACTH-dependent CS; does the patient have Cushing’s disease (a pituitary source of ACTH hypersecretion) or ectopic ACTH syndrome (an extra pituitary source of ACTH hypersecretion).

The consensus guidelines for the diagnosis of endogenous Cushing's syndrome and Cushing's disease are described in details by Arnaldi et al 2003 and Nieman et al 2008 and Lauber et al 2006.

2.2.4 Treatment landscape

Pituitary surgery is the current first-line therapy for Cushing's disease, but even in the hands of experienced neurosurgeons 10-30% of patients with microadenomas and 35-50% of patients with macroadenomas experience persistence of hypercortisolism. Recurrence after initial normalization of cortisol levels occurs in 10-30% of patients, mostly within 5 years of surgery, however recurrence may occur a decade or more after initial successful surgery (Blevins et al 2009). There is no consensus on the therapy for patients in whom the first pituitary surgery fails to control the disease, or patients in whom surgery is not feasible (either due to contraindications to surgery, lack of availability of an experienced neurosurgeon or refusal from the patient). Repeat pituitary surgery may be undertaken if disease persists after initial surgery, although there is an overall lower rate of success than that seen after the first operation. Furthermore, re-operation carries a significant risk of pituitary insufficiency (Biller et al 2008). Hypopituitarism requires complex life-long hormonal replacement therapies necessary for patient survival (Pivonello et al 2008). Treatment usually focuses on replacing the target hormones rather than the pituitary hormones (Swearingen et al 1999).

For patients not cured by pituitary surgery (either one or multiple attempts), irradiation (fractionated external beam radiotherapy or stereotactic radiosurgery) of the pituitary or bilateral adrenalectomy are the remaining non-medical treatment options. Radiotherapy may take many years to be effective, if at all, with little or no predictability of response. Control of hypercortisolism occurs in approximately 50-60% of patients within 3-5 years (Biller et al 2008). However, the procedure also results in hypopituitarism in up to 66% of patients. Late sequelae of either type of radiation therapy are rare and include radiation-induced optic neuropathy, temporal lobe necrosis, increased mortality from cerebrovascular disease, and secondary carcinogenesis (Becker et al 2002, Blevins et al 2009). Although bilateral adrenalectomy results in a definite cure for hypercortisolism, it is associated with life-threatening primary adrenal insufficiency that requires life-long replacement hormonal therapy and monitoring of both glucocorticoids and mineralocorticoids. Additionally, Nelson's syndrome (i.e. enlarging pituitary adenoma following bilateral adrenalectomy) could be a severe complication of bilateral adrenalectomy that requires close medical attention (Assie et al 2007, Biller et al 2008). Therefore, patients not cured by pituitary surgery have limited treatment options and poor outcomes (Hammer et al 2004).

Presently, medical (pharmacological) therapy has a limited role in the management of patients with Cushing's disease. Currently used medical therapies generally fill a short-term, palliative role in patients who are awaiting the therapeutic effects of radiation therapy, or in very ill patients in preparation for surgery (Biller et al 2008, Tritos et al 2011, Fleseriu and Petersenn 2012, Tritos and Biller 2012).

Ketoconazole is an anti-fungal agent that effectively inhibits the synthesis of cortisol, adrenal and gonadal androgens. It is an 11β-hydroxylase and 17α-hydroxylase inhibitor, which leads to a decrease in cortisol production. Published studies on the use of ketoconazole in Cushing's syndrome are small. There are no reported prospective studies on the efficacy of ketoconazole

as monotherapy in patients with Cushing's disease, and the definitions of response vary among reports. The initial efficacy reported in small, uncontrolled studies with ketoconazole (normalization of UFC) is up to 81% of patients with Cushing's disease, however escape has been reported with long-term treatment (Diez and Iglesias 2007, Tritos and Biller 2012, Fleseriu and Petersenn 2012). In a retrospective study (Castinetti et al 2008), the efficacy of ketoconazole (UFC normalization at 2 consecutive determinations) as monotherapy was evaluated in 38 patients. 17 patients (44.7%) had a response after 1-3 months of therapy, 16 were uncontrolled at the end of follow-up, and 5,patients discontinued within the first week of therapy due to intolerance. The most common adverse drug reactions with ketoconazole are gastrointestinal and pruritus. Inhibition of androgen synthesis in men may cause erectile dysfunction, decreased libido and gynaecomastia. Reversible alterations in hepatic tests have been reported in about 10-15% of patients. Rare cases of hepatotoxicity with fatal outcome have been reported (Diez and Iglesias 2007). Ketoconazole is a potent inhibitor of cytochrome P450 enzymes, with significant limitations in its use due to potential DDIs.

Metyrapone is a pyridine which acts by blocking 11β-hydroxylase, thus inhibiting cortisol biosynthesis. There are no large prospective studies on the efficacy of metyrapone as monotherapy. Treatment with metyrapone in combination with radiation therapy or other drugs normalized plasma cortisol in up to 74% of patients with Cushing's disease and Cushing's syndrome (Diez and Iglesias 2007). Reduction of cortisol levels may induce an increase in pituitary ACTH secretion. Therefore, like with other steroidogenesis directed therapies, escape phenomenon is common (Biller at al 2008). Side-effects include nausea, vomiting, skin rash, ataxia, lethargy, dizziness, vertigo, and edema. Inhibition of 11β-hydroxylase by metyrapone coupled with increased ACTH levels causes increased androgenic and mineralocorticoid precursors. This effect may result in hypertension and hirsutism in women (Diez and Iglesias 2007).

Mitotane has been used in the treatment of adrenocortical carcinomas due to its adrenolytic action. It also is an inhibitor of 11β-hydroxylase, 18-hydroxylase and 3β-hydroxysteroid dehydrogenase. Data are limited as there are no reported large prospective studies on the use of mitotane in patients with Cushing's disease. In combination with radiation therapy, remission rates have been seen in up to 81% of patients in small, uncontrolled studies (Diez and Iglesias 2007). The onset of action of mitotane is slow and effects may be delayed between 6 and 8 weeks. It has a prolonged half-life and it accumulates in adipose tissue and adrenal glands. The adrenolytic effect of mitotane can last for a long time after the drug is stopped and in some cases mitotane causes irreversible primary adrenal insufficiency. Gastrointestinal and neurological toxicity are significant limitations to its use. Anorexia, nausea, vomiting and diarrhea are common. At higher doses, neurological side effects are common and include abnormal gait, dizziness, vertigo, confusion and problems with language expression.

Recently, **mifepristone (Korlym),** a glucocorticoid receptor blocker, was approved by the FDA for the treatment of hyperglycemia in patients with Cushing's syndrome with impaired glucose tolerance or diabetes mellitus. Results from a prospective, multicenter study by Fleseriu et al (2012) show that after 6 months of therapy in 29 patients with impaired glucose tolerance or diabetes at baseline, 60% of patients had at least a 25% decrease in the glucose area-under-the-curve during and oral glucose tolerance test, and that HbA1c decreased significantly from 7.43% to 6.29%. Among the 46 patients in the modified ITT analysis, the

mean weight change was -5.7%. Insulin resistance, depression, cognition, and quality of life also improved. Common AEs in this study were fatigue, nausea, headache, low potassium, arthralgia, vomiting, edema, and endometrial thickening in women.

Because mifepristone increases ACTH and cortisol levels, efficacy can only be assessed clinically. Similarly, the diagnosis of adrenal insufficiency has to be made in the absence of a reliable cortisol biomarker. As mifepristone blocks only the glucocorticoid receptor, the mineralocorticoid activity of cortisol excess can lead to hypokalemia and hypertension in some patients. It is conceivable that corticortroph tumor progression is similar with that seen in patients after bilateral adrenalectomy, but long term data are not available. Because of its antiprogesterone effects, chronic mifepristone use in women may result in unopposed estrogenic stimulation of tissues, resulting in endometrial thickening or unexpected vaginal bleeding. Finally, Addisonian crises have been reported with mifepristone (Assie et al 2007, Diez and Iglesias 2007, Fleseriu et al 2012).

Cabergoline is a dopamine receptor agonist used for the treatment of prolactinomas and (at high doses) Parkinson's disease. The rationale for the use of cabergoline in Cushing's disease is the expression of dopamine receptors in some corticotroph pituitary adenomas (Biller et al 2008). Two small studies on the use of cabergoline as monotherapy have been reported (Pivonello et al 2009, Godbout et al 2010), as well as some retrospective studies and case reports in patients with ACTH-dependent Cushing's syndrome (Villar et al 2012, Diez and Iglesias 2007). In the prospective, single center study by Pivonello et al, 20 patients with Cushing's disease were treated with cabergoline. Of 15 patients with normalization of UFC, 8 patients (40%) maintained response for at least 12 months, whereas 5 patients lost response after 6-18 months. The main side effects were hypotension and asthenia, which led to discontinuation of 2 patients. In a retrospective study in 30 patients with Cushing's disease by Godbout et al, 37% of patients achieved a response. Note that selection bias (i.e. patients with dopamine-receptor positive adenomas) cannot be ruled out in these studies.

In summary, despite many years of experience in the medical management of Cushing's disease, many patients cannot be controlled effectively long term. Therefore, a medical therapy that acts directly on the pituitary tumor to normalize ACTH and cortisol levels, that controls tumor growth, and improves patients' quality of life and overall survival and that has been systematically studied in prospective randomized studies would represent a major advance in the treatment of this disease by filling a large unmet medical need in this patient population (Biller et al 2008, Tritos et al 2011, Fleseriu and Petersenn 2012).

2.3 Pasireotide

2.3.1 Rationale for development in Cushing's disease

Pasireotide is a second-generation analog of the natural peptide hormone somatostatin. Native somatostatin exerts its biological activity by binding to SSTRs, of which there are 5 known receptor subtypes (SSTR 1 through 5). Somatostatin and SSTR receptors are widely distributed in the human body and are important regulators of endocrine and exocrine secretion, affecting the regulation of many hormones such as GH, glucagon, insulin, gastrin, secretin, and thyroid-stimulating hormone (Reichlin 1983).

Two analogs of somatostatin, octreotide and lanreotide, have been developed and are currently widely used in acromegaly and for symptomatic control of neuroendocrine tumors. The binding profile of these analogs differs significantly from that of natural somatostatin. While somatostatin binds equally avidly to all 5 SSTR subtypes, octreotide and lanreotide bind preferentially to SSTR2 and, to a lesser extent, to SSTR3 and SSTR5 (Schmid and Schoeffter 2004). Neither octreotide nor lanreotide are effective in the treatment of Cushing's disease (Pivonello et al 2008).

In vitro studies have shown that corticotroph tumor cells from Cushing's disease patients express high levels of SSTR5, whereas the other receptor subtypes are either not expressed or are expressed at a significantly lower level (Batista et al 2006). In addition, SSTR2 receptors on corticotroph cells are down-regulated in the presence of high levels of glucocorticoids, while SSTR5 receptors are not affected (Hofland 2005, van der Hoek 2004). Cushing's disease patients have high levels of circulating cortisol, which potentially leads to a reduced expression of SSTR2 receptors. This may explain why currently available somatostatin analogs lanreotide and octreotide, which bind preferentially to SSTR2, have shown poor efficacy in treating Cushing's disease.

Pasireotide has a broader receptor binding profile than either octreotide or lanreotide. It has moderate-to high binding affinity and functional activity for SSTRs 1, 2, 3, and 5, and little affinity for SSTR4 (Table 2-1; Bruns et al 2002, Schmid and Shoeffter 2004).

Because pasireotide's affinity for SSTR5 is high, it was postulated that it would be effective in the treatment of Cushing's disease by inhibiting the release of ACTH and consequently decreasing adrenal corticosteroid production. Indeed, preclinical studies showed that pasireotide inhibits ACTH secretion from human corticotroph adenomas in vitro with a greater effect than octreotide (Hofland et al 2005). In vivo studies in rats also showed a stronger inhibitory effect of pasireotide on stimulated secretion of ACTH and corticosterone than octreotide (Silva et al 2005).

Table 2-1 Receptor binding affinity of somatostatin and analogs

	Receptor binding affinity (IC_{50} nmol/L)					
	SSTR1	**SSTR2**	**SSTR3**	**SSTR4**	**SSTR5**	**t1/2 (h)**
Somatostatin	0.9	0.2	0.6	1.5	0.3	≤ 0.05
Octreotide	280	0.4	7.1	>1000	6.3	2
Lanreotide	180	0.5	14	230	17	<1
Pasireotide	9.3	1.0	1.5	>1000	0.2	12

Bruns et al (2002), Eur J Endocrinol; 146:707-716, Gillespie et al (1998) J Pharmacol Exp Therap; 285:95-104

3 Regulatory history

USA

In May 2006 Novartis consulted with the Division of Metabolism and Endocrinology Products of the FDA on the proposed design of the Phase III clinical development program for the treatment of Cushing's disease at an End-of-Phase 2 (EOP2) meeting. Subsequent to the EOP2 meeting Novartis submitted the protocol for Special Protocol Assessment (SPA) in October 2006. Although no formal SPA agreement is in place, all the comments received

from the Division in context of the SPA were considered and the majority of comments were implemented. Concurrence was obtained on the design of the Phase III study B2305 shown in Figure 7-1, including the choice of the primary efficacy endpoint (normalization of UFC levels after 6 months of treatment), the method for assessing the primary efficacy variable (four 24-h baseline UFC measurements over a 2-week period to assess baseline, and requiring at least 4 samples over 2 weeks for UFC measurement at key time points whilst 2 samples over 2 weeks were recommended at other time points as not to adversely affect patient compliance and retention), duration of the study (patients were followed for a total of 12 months in the core phase of the study to evaluate maintenance of response), and the dose titration scheme. In addition, the Division supported that the study should comprise two treatment arms investigating different doses of pasireotide, and that the absence of a placebo arm was justified due to ethical considerations, however the discussion on the dose levels to be used in the treatment arms was not completed. The Division also agreed that the inclusion and exclusion criteria are adequate to define the target population.

The SPA discussion also covered the overall statistical analysis plan, including the acceptability of the definition of the primary endpoint of UFC normalization. In this context Novartis proposed the response rate of 15%, which was agreed upon by an external Cushing's disease Advisory Board and the B2305 Study Steering Committee as it was considered to be clinically meaningful in this setting, given the lack of approved medications, and more importantly the lack of medications that can be used long-term with demonstrated efficacy and safety, and the fact that UFC rarely spontaneously normalized. Novartis agreed to collect objective data to support the primary endpoint, such as improvement of hypertension, hyperglycemia, hyperlipidemia, weight, osteoporosis, bruisability, and other clinical manifestations of Cushing's disease, and that blinded assessments were to be performed for subjective signs of Cushing's disease that are evaluated using photographs, the bone mineral density analyses, and the pituitary tumor volume measurements.

Agreement was obtained on the adequacy of the preclinical safety program and the proposed clinical pharmacology development plan at the EOP2 meeting. The safety assessments in study B2305 were refined, including close monitoring and treatment plan of patients with diabetes, ECG monitoring, and other safety assessments.

Overall, the Division noted that the single Phase III study B2305 was adequate to support approval, provided there is substantial convincing evidence that decreases in UFC did not occur spontaneously and that there are no concerning safety signals.

All possible comments received from the Division in context of the SPA were implemented, however the revised protocol was not re-submitted to the FDA for final agreement.

Novartis met with the FDA at a pre-NDA meeting in August 2010 to agree on the content of the NDA. NDA 200677 was filed with FDA on 21-Jun-2011. The application was withdrawn on 19-Aug-2011 after Novartis identified a quality issue with stability commitment batches of the pre-filled syringe primary packaging. Written agreement was received from the FDA in November 2011 on the proposed revised quality package which Novartis proposed in a Type C Meeting Request. NDA 200677 was resubmitted to the FDA on 17-Feb-2012 with a revised drug product section to support the registration of the ampule drug product which had been used in the clinical development program.

Orphan designation

Due to the low prevalence of Cushing's disease in the US, pasireotide was granted Orphan drug status by the FDA for this indication on 24-July-2009.

European Union

Scientific advice was sought from the Committee for Medicinal Products for Human Use (CHMP) before initiation of the Phase III study B2305 (EMEA/H/SA/730/1/2006/II) in parallel to the End or Phase 2 discussion with the FDA in July 2006.

Changes introduced based on the European Medicines Agency (EMA) advice included a change to a two arm design, an increase in the sample size, change in the definition of primary efficacy response (to normalization of UFC without dose increase) and a change in the criteria for dose increase. The revised protocol with changes based on FDA and EMA feedback was submitted to the FDA for SPA (see USA Regulatory history section).

On 19-Jan-2012, the CHMP adopted a positive opinion recommending the granting of a Marketing Authorization for pasireotide (Signifor®) for the treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed (starting dose 600 µg b.i.d. s.c. with optional dose increase to 900 µg b.i.d. and dose decrease to 300 µg b.i.d.). The European Commission granted pasireotide marketing approval in the EU on 24-Apr-2012.

4 Overview of non-clinical development

The nonclinical profile of pasireotide has been characterized in a comprehensive testing program that included in vitro and in vivo studies in mice, rats, rabbits and monkeys. These studies include pharmacology studies, non-clinical ADME studies, and toxicology studies (including acute, subchronic and chronic toxicity studies, carcinogenicity studies in transgenic mice, local tolerance studies, reproduction studies, as well as in vitro and in vivo genotoxicity studies). Most of these studies were performed using the s.c. route of administration. The long acting release formulation, with monthly intramuscular administration of pasireotide LAR has been evaluated over extended periods for local tolerance and toxicokinetic in rats and rabbits. Finally, the toxicity of an oral formulation has been tested in rats and monkeys, and i.v. administration is being used to assess the bioavailability in monkeys. All pivotal toxicology studies were conducted according to Good Laboratory Practice (GLP).

4.1 Pharmacology

Somatostatin analogs like octreotide are currently the standard of care for patients with acromegaly and for patients with symptoms of gastroenteropancreatic neuroendocrine tumors (GEP-NETs). In patients with primary Cushing's disease, octreotide was not effective (de Herder 1996). It was shown recently that ACTH-secreting pituitary adenomas from Cushing's patients predominantly express SSTR5 and also SSTR2 and SSTR1 receptors. Based on this receptor expression profile and the high affinity of pasireotide for SSTRs 1,2,3 and especially SSTR5, there is good scientific rationale to support the possible effectiveness of pasireotide in Cushing's disease.

4.1.1 Primary and secondary pharmacology

The preclinical studies investigating primary or secondary pharmacology were performed using state of the art technologies. The general properties of pasireotide on hormone secretion were characterized in a series of studies in vitro and in vivo showing the antisecretory and antiproliferative efficacy of the compound. The properties of pasireotide on hormone secretion were studied in AtT20 cells. This cell line is the only ACTH-secreting cell line derived from a mouse pituitary tumor, and expresses SSTR2 and SSTR5. Furthermore, the corticotropin releasing hormone (CRH) stimulated secretion of ACTH from this cell line has been shown to be inhibited by natural somatostatins (SRIF-14 and SRIF-28) as well as by SSTR specific agonists (Hofland et al 2005), (Strowsky et al 2002). Thus this cell line has several characteristics which are also found in primary pituitary tumor cells from Cushing's patients (Batista 2006). Although the well characterized mouse AtT20 cell line was very helpful to establish the optimal conditions to study the in vitro efficacy of pasireotide, it was considered a necessity to demonstrate in vitro efficacy in pituitary cells derived from patients with Cushing's disease, also because human pituitary cell lines secreting ACTH are not available. Due to the low prevalence of patients with primary Cushing's disease and the necessity to obtain sufficient numbers of viable cells from usually small pituitary tumors, these studies on freshly obtained tumor samples could only be conducted in specialized clinical centers. Therefore, the in vitro studies on freshly isolated cells from patients with primary Cushing's disease were conducted in the laboratory of Profs. Lamberts and Hofland (Erasmus University, Rotterdam, The Netherlands) and the effects on proliferation and ACTH secretion were conducted mainly in the laboratory of Prof. Klibanski (Harvard Medical School, Boston, Massachusetts) (Hofland et al 2005) and (Batista et al 2006). Both laboratories are specialized in the conduct of research on the action of somatostatin and its analogs and have investigated the effect of octreotide on ACTH secretion in vitro and in patients with Cushing's disease. In vivo studies investigating the effects of pasireotide on ACTH and corticosterone release in rats were conducted by Novartis. These studies required special equipment which allowed the stress free stimulation of ACTH release and repeated blood sampling in freely moving catheterized rats.

4.1.2 Safety Pharmacology

In accordance with ICH guidelines S7A and S7B, a full set of safety pharmacology studies was conducted to assess the safety of pasireotide in particular organ systems. The studies were conducted by Novartis or at a research organization under contract to Novartis.

Pasireotide did not affect the respiratory system. As expected from its pharmacological action, alterations of general and neurobehavioral activities were observed in mice at 15 mg/kg.

Preclinical studies did not identify any potential for pasireotide to delay ventricular repolarization (QT interval prolongation). Electrophysiology data from the hERG channel assay revealed no inhibition of the hERG tail currents up to 30 µM (31.42 µg/mL) and pasireotide did not exert any electrophysiological effects on rabbit Purkinje fibers up to the concentration of 30 µM (31.42 µg/mL). A single dose telemetry study in male monkeys, after s.c. administration of pasireotide at doses up to 1.6 mg/kg, showed no effect on cardiovascular function. It is to be noted that the exposure (Cmax) at the top dose of 1.6 mg/kg used in the

monkey study is approximately 77-103 fold higher than in humans administered 900µg pasireotide b.i.d.

In addition to the standard cardiovascular assays, the potential effects of pasireotide on major ion cardiac channels (potassium (KCNQ1 and sKv3.4/Kir3.1) sodium (Nav1.5) and calcium (Cav1.2) channels) were also assessed. No interference with any of the examined channels was seen at concentrations up to 30 µM (31.42 µg/mL). Furthermore, in general toxicology studies with monkeys (up to 39 weeks), no ECG changes were seen at any dose (up to 6.4 mg/kg for 4-weeks, and up to 3.2 mg/kg/day for 39-weeks).

4.2 Non-clinical ADME studies

Following s.c. injection in rat, mouse, rabbit, and monkey, the absorption of pasireotide was rapid (T_{max}: 0.5-2 hr). The absolute bioavailability from pre-clinical studies in rats (107%) and monkeys (102%) was complete. The distribution of pasireotide between blood cell and plasma showed that pasireotide was primarily located in the plasma component (99%, 87% and 91% for rat, dog and human, respectively), and distribution in blood was independent of concentrations. Plasma protein binding of pasireotide was independent of concentration, and the protein-bound fraction was 94%, 93% and 88% in rat, dog and human plasma, respectively. In rats, pasireotide was mainly distributed in the liver, kidney, cartilage, lymph nodes, and spleen. Pasireotide was highly metabolically stable in rat, monkey and human liver microsomes, rat hepatocytes, and human kidney microsomes. Unchanged pasireotide was the major circulating component in the plasma of rat (93-95% of AUC) and monkey (93% of AUC). In rat and monkey studies, the excretion of total radioactivity was predominantly in the feces (~75% in rat and ~95% in monkey) with renal elimination of 6-9% of dose.

4.3 Toxicology studies

A complete toxicology safety evaluation program (subacute, chronic, reproductive toxicology studies, genotoxicity, carcinogenicity, and phototoxicity studies) was conducted to support the chronic administration of pasireotide to patients. The toxicology program was consistent with the ICH M3 Guideline of the Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals as well as all other relevant ICH Guidelines on Safety. The s.c. route of exposure was chosen because it is the clinical route in humans. All principal toxicology studies were performed in accordance with GLP and currently accepted guidelines with respect to animal numbers and dose levels used. These studies were conducted either at a Novartis facility or at a research organization under contract to Novartis.

In general dose toxicity studies, the tolerability of pasireotide was species dependent, with dogs being the most sensitive species, experiencing severe GI symptoms leading to discontinuation of dosing. Because the poor GI tolerability in dogs (which was considered species- specific, as both monkey and humans tolerated higher exposures), the monkey was selected as the primary non-rodent test species. Due to the good tolerability of pasireotide in monkeys, the duration of the chronic studies was extended from 26 to 39 weeks. In monkeys, histopathology findings were observed in the pituitary (increases acidophils), thyroid (small follicles), large intestine (distension of large GI, with proteinaceous material present in the crypts of the mucosa in the caecum and colon) and injection sites (inflammation, fibrosis, hemorrhage). Reduced hematopoietic activity was also evident in short term studies, as shown

by the reduced hematopoietic cellularity in the bone marrow in short term studies (not observed in the chronic study). The systemic findings are considered to be related to pharmacological activity of somatostatin analog. Such pharmacological activities included inhibition of GH secretion in pituitary gland (Weckbecker 2002), inhibition of TSH release by thyroid gland (Barnett 2003), suppression of GI motility (Gyr 1993), and reduction of hematopoietic activity (Van Hagen 1994, Weinstock 2000). A no observed adverse effect level (NOAEL) of 1.6 mg/kg was identified for the 39 week study, allowing a wide safety margin when comparing to human exposure values.

With pasireotide treatment in rats, reduced body weight and body weight gain was observed at doses ≥ 0.04 mg/kg after 2 weeks and ≥ 0.008 mg/kg after 26 weeks. Most of the biochemical alterations identified in serum chemistry (such as reduction in cholesterol, triglyceride and α 1-globulin) together with the suppressed body weight development, is consistent with the direct effects of GH on hepatic lipid metabolism (Fan 2009) and somatostatin-related reduction in dietary utilization that has been attributed to reduced gut motility and changes in the feeding behavior of rats (Scalera 1998) and is considered secondary to the effects of pasireotide on endocrine secretions. Slight and reversible changes in coagulation parameters (PT and APTT) were observed only in female rats in the 26 weeks study, a finding not associated with histopathology modifications in the liver and isolated to this study. As monkeys exposed to higher pasireotide levels did not exhibit such a coagulation change, and no clinically meaningful change of coagulation parameters were observed in humans, this finding is not considered toxicologically important. In addition to the expected pharmacological effect on the pituitary gland (decreased eosinophilia of the somatotrophs), pasireotide also reduced cellularity in the hematopoietic component seen in the bone marrow and spleen in treated rats. This is believed to be due to binding of pasireotide to SSTRs on lymphocytes, monocytes and hematopoietic precursors (CD34+ cells), resulting in inhibition of cell proliferation, a well described function of somatostatin (Van Hagen 1994; Weinstock 2000). It is also known that insulin-like growth factor 1 (IGF-1) plays a stimulatory role in erythropoiesis (Mirza 1997). The lower IGF-1 levels after pasireotide administration might have contributed to the inhibition of hematopoiesis. The inhibitory effects on the female genital tract and estrus cycles were observed across rat studies. These effects are considered to result from the pasireotide-induced decrease in IGF-1 as IGF-1 is necessary to the priming actions of estradiol in the female neuroendocrine reproductive axis (Etgen 2006) prior to ovulation.

Reversible increases in liver enzymes (ALT, AST), and alkaline phosphatase (ALP)) were observed in most rodent studies, typically at higher doses. No histopathological findings of liver injury were observed in any studies. Minor findings reported in rats included decreased liver weights.

It is noted that the toxicological test species (mouse, rat, and monkey) were adequately and dose-dependently exposed to pasireotide. There was in general no gender difference and the drug did not accumulate following multiple injections. At the NOAEL (0.024 mg/kg/day pasireotide x 26 weeks in rats; 1.6 mg/kg/day x 39 weeks in monkeys) in long-term toxicology studies, plasma exposure (AUC) in rats and cynomolgus monkeys was 0.15- and 39-fold the exposure (AUC) reached at the human therapeutic dose of 900 µg b.i.d. in healthy volunteers. It should be noted that at the high-dose of chronic toxicity studies (0.24 mg/kg/day in rats and 3.2 mg/kg/day in monkeys) plasma exposure (AUC) in rats and cynomolgus

monkeys was 8.2- and 306-fold that same human exposure (AUC) demonstrating large margins of safety, and most of the findings in the high dose reflected the exaggerated pharmacological effects of pasireotide in rodents.

The findings observed in the reproductive and developmental toxicity studies are also consistent with exaggerated pharmacology. Briefly, as expected, body weight and food intake parameters were affected in F_0 adults and extremities showed swelling at high doses. Decreased female fertility, characterized by abnormal estrus cycles and reduced litter size was observed at all doses in rats. Fertility was not affected in males administered up to 10 mg/kg/day, the highest dose tested. Pasireotide was not teratogenic in rabbit or in rat. In rats, slightly increased incidence of mal-rotated limbs (which also occurred in controls) were only observed at maternally toxic doses. Increased early and/or total resorption and decreased fetal weights were noted in both species and are considered a consequence of maternal toxicity. The abortions observed in rabbits are also considered secondary to maternal toxicity at a dose that produced mortality. In the pre- and postnatal development (PPND) study, slower development was characterized by lower body weights and the ensuing delay in pinna unfolding. The lower body weight gain observed in the pups during lactation is probably due to the effect of pasireotide on the lactating dams as body weight gains became similar across control and pasireotide-dosed groups after weaning and there was no permanent effect on functional or behavioral endpoints.

The typical starting age for animals in the general toxicology studies are as young adults (8- to 9-weeks old for rats and 2- to 4-years old for monkeys). No juvenile toxicity study was conducted because the pediatric population is not part of the intended clinical population.

Pasireotide did not cause genotoxicity. The carcinogenicity studies in rats and transgenic mice did not identify any carcinogenic potential. The high dose of the carcinogenicity studies in rat and mice are associated with significant safety margins compared to human systemic exposure.

The local tolerability of the s.c. formulation was good, although mild to moderate irritation and degeneration of tissue adjacent to the injection site was observed in all animal species tested at high concentrations (2 mg/mL or above), whereas concentrations of 0.7 mg/mL or lower were locally well tolerated. Multiple s.c. injections at the same site within short time periods should be avoided in man.

There was no evidence of skin or eye irritation potential in rabbits.

In conclusion, the large body of preclinical safety data obtained so far supports the administration of pasireotide in clinical settings. The pre-clinical findings were primarily related to the pharmacologic actions of pasireotide and provided the basis for safety monitoring in clinical studies.

5 Overview of clinical pharmacology

5.1 Pharmacokinetics

5.1.1 Pharmacokinetic studies

Clinical pharmacology studies with pasireotide s.c. in healthy volunteers, subjects with varying degrees of hepatic impairment (mild, moderate, and severe), and patients with Cushing's disease are summarized in Table 5-1.

Table 5-1 Summary of Clinical Pharmacology Phase I studies and Phase II and III studies with PK/PD components included in the NDA

Study	Objectives	Pasireotide s.c. Dose	No. of subjects
Phase I healthy volunteer studies			
B2101	Safety, tolerability, PK, PD	1, 2.5, 10, 30, 100, 200, 300, 600, 1200 µg single dose	72
B2102	Safety, tolerability, PK, PD	50, 200, 600 µg q.d. x 14 days	33
B2106	Safety, tolerability, PK	900, 1200, 1500 µg single dose 450, 600, 750 µg b.i.d. x 1 day	17
B2107[a]	Safety, tolerability	150, 300, 600, 900, 1200, 1500 µg q.d. x 8 days 150, 300, 450, 600, 750 µg b.i.d, x 8 days	66
B2108	Safety, tolerability, PK	450, 900, 1350, 1800, 2025, 2250 µg/day continuous infusion x 7 days	44
C2101	Safety, tolerability, PK	300 µg single dose	78
B2112	ADME, PK, safety	600 µg single dose	4
B2113	Cardiac safety (QT/QTc), PK, PD	Part I: 900, 1200, 1500, 1800, 1950, 2100 µg b.i.d. x 5 days Part II: 1950 µg b.i.d. x 5 days	128
B2124	Effect of antihyperglycemic drugs on glucose metabolism (glucose, insulin, glucagon), PK	600 µg b.i.d, x 7 days	90
B2125	Cardiac safety (QT/QTc), PK, PD	600, 1950 µg b.i.d, x 5 days	112
B2216	Blood glucose, PD, safety	600, 900, 1200 µg b.i.d, x 8 days	38
Phase I study in subjects with hepatic impairment			
B2114	Hepatic impairment, PK, safety	600 µg single dose	34
Phase II and Phase III studies with PK/PD components in patients with Cushing's disease			
B2208	Efficacy, safety, PK, PD	600 µg b.i.d. x 15 days	39
B2208E1	Efficacy, safety, PK, PD	300-900 µg b.i.d.; dose change allowed	19
B2305	Efficacy, safety, PK, PD	300, 600, 900, 1200 µg b.i.d.; dose change allowed	162

5.1.2 Absorption, distribution, metabolism, excretion

In healthy volunteers, results from the human ADME study B2112 with a single s.c. dose of 600 µg ^{14}C-labelled pasireotide showed that 55.9 ± 6.63% of the radioactivity dose was recovered over 10 days post-dose, including 48.3 ± 8.16% of the radioactivity in feces and 7.63 ± 2.03% in urine, mainly as the unchanged form. These data indicate that pasireotide is

mainly eliminated via hepatic clearance; with renal clearance making only a small contribution to the elimination of pasireotide in man. No circulating metabolite was detected.

Following single-dose and multiple-dose s.c. administrations of pasireotide in healthy volunteers, the PK of pasireotide s.c. demonstrated rapid absorption (T_{max}: 0.25-0.5 h), with extensive distribution (V_z/F >100 L), and low clearance (CL/F ~7.6 L/h). The AUC accumulation ratio of pasireotide to steady-state is moderate (approximately 20 to 40% increase over the first-dose data) upon once daily dosing for 14 days. Based on the AUC accumulation ratio, the calculated effective half-life ($t_{1/2,eff}$) for pasireotide s.c. is approximately 12 h.

In blood, pasireotide is primarily located in the plasma component (91%), and distribution in blood is independent of concentration. The extent of plasma protein binding is moderate (88%) and concentration-independent at therapeutic plasma levels (i.e. predicted $C_{max,ss}$ < 0.1 µM or <100 ng/mL) in patients with Cushing's disease. DDI due to protein-binding displacement is not expected to occur.

At therapeutic dose levels, pasireotide is not a substrate, inhibitor, or inducer of CYP450 (cytochrome P450) enzymes; not an inhibitor of UGT1A1 (uridine diphosphate glucuronosyltransferase); not a substrate of BCRP (breast cancer resistance protein), or hepatic uptake transporters such as OCT1 (organic cation transporter 1) or OATP (organic anion-transporting polypeptides) 1B1, 1B3 and 2B1; not an inhibitor of OATP1B1, OATP1B3, BCRP or P-gp (P-glycoprotein). Pasireotide is likely to be a substrate of P-gp, but P-gp may not play a significant role in the absorption, distribution or elimination of pasireotide in humans.

In vitro results showed weak inhibition of MRP2 (multi-drug resistance protein 2) and BSEP (bile salt export pump) by pasireotide with an IC_{50} value of about 10 µM, which is more than 100-fold higher than the predicted $C_{max,ss}$ (<0.1 µM or <100 ng/mL) in patients with Cushing's disease receiving a dose of 900 µg b.i.d. Although the intracellular concentration of pasireotide in human hepatocytes is difficult to ascertain, the concentration of pasireotide in liver is not expected to be high in human because the ratio of liver concentration over plasma concentration is only ~2.3-fold in rat (calculated based on the liver/blood ratio = 4.6 at liver T_{max} and blood/plasma ratio = 0.5). Therefore, the likelihood of pasireotide inhibition on MRP2 and BSEP in human is expected to be low, which is consistent with the low incidence of elevated bilirubin (see Table 8-14). However, it is possible that relevant inhibition could occur on rare occasion in patients who have a genetic pre-disposition, potentially coincident with higher exposure of pasireotide in the liver.

No first-pass effect or food effect is expected for pasireotide s.c. because the formulation is administered via parenteral route.

5.1.3 Drug-drug interactions

Based on data from protein binding, metabolism and transporter studies mentioned above (Section 5.1.2), the likelihood of DDI between pasireotide and co-medications is low in patients. To confirm this, a DDI study (B2127) is ongoing to evaluate the effect of verapamil (as P-gp inhibitor) on PK of pasireotide s.c. (as P-gp substrate) in healthy volunteers.

In dogs, pasireotide was found to decrease blood level of cyclosporine by reducing its intestinal absorption. It is unknown whether this interaction in dogs translates into humans; therefore dose adjustment of cyclosporine may be required with pasireotide co-administration.

Limited published data suggest that somatostatin analogs might have an indirect effect in decreasing the metabolic clearance of compounds metabolized by CYP450 enzymes, via suppression of GH secretion (Rasmussen et al 1998). Available data can not exclude the possibility that pasireotide may exert such an indirect effect, therefore caution should be taken when pasireotide is administered concomitantly with drugs possessing a low therapeutic index and which are metabolized mainly by CYP3A4 (e.g. quinidine).

Limited literature with other somatostatin analogs (e.g. octreotide) suggest that co-administration with bromocriptine may increase the availability of bromocriptine (Flogstad et al 1994).

Caution is required when co-administering pasireotide with anti-arrhythmic medicines and other drugs that may prolong the QT interval.

5.1.4 Pharmacokinetics in patients with Cushing's disease

In population pharmacokinetic (PopPK) modeling analysis, the clearance of pasireotide in patients with Cushing's disease was found to be lower (CL/F ~3.8 L/h) (pooled datasets from studies B2305 and B2208) than in healthy volunteers (CL/F ~7.6 L/h) (pooled datasets from studies B2101, B2102, B2016, B2108 and C2101), indicating a 2-fold higher exposure in patients compared to healthy volunteers. It should be note that these values of CL/F refer to a "typical" (i.e. population mean) patient and a "typical" healthy volunteer, whereas the two populations differed in population mean values of age and lean body weight, as well as gender ratio. The PopPK modeling found that CL/F was influenced by age and lean body weight in the analysis of Cushing's disease patients, and influenced by age in the analysis of healthy volunteers. Cushing's disease patients tended to be older than the healthy volunteers (population mean values of age were 41 years for patients and 29 years for healthy volunteers). In addition, patients were mostly female, and healthy volunteers included in the PopPK analysis were all males; therefore patients tended to have lower lean body weight than healthy volunteers (population mean values of lean body weight were 51 kg for patients and 62 kg for healthy volunteers). According to the PopPK model, if a patient had the same "typical" values of gender (male), age (29 years) and lean body weight (62 kg) as a "typical" healthy volunteer he would have CL/F ~4.8 L/h, indicating a 1.6-fold higher exposure in patients than healthy volunteers. The still unexplained 60% difference (i.e. 1.6-fold after demographic adjustment of gender, age and lean body weight) between patients and healthy volunteers might be due to disease-related factors, such as reduced bile flow accompanying fatty liver in patients with Cushing's disease

In response to a request from the FDA, an additional PopPK analysis was done on data pooled from healthy volunteers and patients with Cushing's disease. That model estimated that patients have a 1.69-fold higher exposure compared to healthy volunteers, consistent with the previous Pop PK analysis results mentioned above.

In study B2208, inter-patient variability was 52-71% for C_{min}, 32-56% for C_{max}, and 31-39% for $AUC_{0\text{-}8hr}$ in patients with Cushing's disease. Intra-patient variability of PK parameters

(C_{min}, C_{max} and AUC_{0-8hr}) was similar between male and female patients (19-26% across all PK parameters).

In study B2305, inter-patient variability was 38-87% and intra-patient variability was 37-54% for C_{min} in patients with Cushing's disease.

5.1.5 Pharmacokinetics in special populations

5.1.5.1 Subjects with impaired hepatic function

Pasireotide exposure is increased in subjects with hepatic impairment. The severity of hepatic impairment (mild, moderate, and severe) correlated with the extent of changes in pasireotide PK parameters. In comparison to subjects with normal hepatic function, patients with mild, moderate and severe hepatic impairment based on Child-Pugh classification had 8%, 60% and 79% increase in AUC_{inf}; 7%, 43% and 67% increase in AUC_{last}; 7%, 67% and 69% increase in C_{max}; and 7%, 37% and 44% decrease in CL/F.

Based on these results, the maximum dose for patients with Cushing's disease with moderate hepatic impairment is 600 µg b.i.d., with a starting dose of 300 µg b.i.d. Pasireotide use in patients with severe hepatic impairment is not recommended, given that exposure in patients with Cushing's disease is higher than in healthy volunteers, and 69 to 79% higher in subjects with severe hepatic impairment compared to normal hepatic function.

Elevations of liver enzymes and total bilirubin have been observed throughout the clinical study program. Patients with severe hepatic impairment may be intrinsically more sensitive to liver enzyme and bilirubin elevations seen as side effects of pasireotide s.c. As a precautionary measure, patients with Cushing's disease and severe hepatic impairment should not be treated with pasireotide s.c.

5.1.5.2 Subjects with impaired renal function

Results from the human ADME study B2112 demonstrated that renal clearance of pasireotide represents a small fraction of the total body elimination (Section 5.1.2). Based on population PK analysis with a pooled dataset from studies B2208 and B2305, mild renal impairment was not found to be a relevant factor influencing pasireotide exposure in patients with Cushing's disease. Therefore, changes in renal function are not anticipated to lead to clinically relevant changes in total or unbound pasireotide levels. As such, dose adjustment should not be required for patients with renal impairment. Even though renal impairment is not expected to have an impact on pasireotide PK parameters, a renal impairment study B2126 has been initiated and is currently ongoing.

5.1.5.3 Age

Age is inversely correlated with CL/F and is positively correlated with volume of the central compartment (V_2/F), both in healthy volunteers and Cushing's disease patients. Population PK simulation predicts that in the observed age range of 18-73 years, the AUC_{ss} ranges from 86% to 110% of that of the typical patient of 41 years. The maximal covariate effect of age on AUC_{ss} was in the same order of magnitude as the standard deviations induced by inter-individual variability (e.g., 25% for CL/F). This suggests that the covariate effects of age on

PK are not clinically relevant. As such, dose adjustment by age is not required for patients with Cushing's disease.

5.1.5.4 Body weight

Body weight is positively correlated with total body clearance (CL/F) and distribution volume (V_2/F), with lean body weight having an even higher correlation. Population PK simulation predicts that in the observed lean body weight range of 33-83 kg the AUC_{ss} ranges from 67% to 134% of that of the typical patient of 49 kg. The maximal covariate effect of body weight on AUC_{ss} is in the same order of magnitude as the standard deviations induced by inter-individual variability (e.g., 25% for CL/F). This suggests that the covariate effects of body weight on PK are considered not to be clinically relevant. As such, dose adjustment by body weight is not required for patients with Cushing's disease.

5.2 Pharmacokinetics/Pharmacodynamics

5.2.1 PK/PD studies for efficacy and safety

The PK/PD relationship between pasireotide exposure and UFC was examined in 2 studies in patients with Cushing's disease (B2208 and B2305; Table 5-1) and results presented in Section 5.2.2.

The PK/safety relationship between pasireotide exposure and FPG and HbA1c levels was explored based on data from study B2208 and study B2305 in patients with Cushing's disease. In addition, data from study B2216 and study B2124 in healthy volunteers provide insight into the mechanism of hyperglycemia associated with pasireotide treatment, and the use of antihyperglycemic agents in the management of hyperglycemia (Table 5-1). The results are presented in Section 8.3.3.

The PK/safety relationships between pasireotide exposure and LFTs (i.e. ALT and total bilirubin), were explored with data from studies B2113, B2125, and B2124 in healthy volunteers, and study B2305 in patients with Cushing's disease (Table 5-1). The results are presented in Section 8.4.3.

Finally, PK/safety analyses for QT/QTc data are available from 2 TQT studies in healthy volunteers (Study B2113 and Study B2125; Table 5-1) and results are presented in Section 8.5.1. The results for simulated ddQTcI (i.e. QTcI change from baseline compared to placebo) in patients with Cushing's disease are presented in Section 8.5.3.

5.2.2 PK/PD for UFC in patients with Cushing's disease

The PK/PD relationship between pasireotide exposure and UFC has been assessed by two different approaches in study B2305: a logistic regression based on UFC response related to trough concentrations from all patients at Month 3 (i.e. before dose increase was allowed), and an analysis using an inhibitory E_{max} model using all data (i.e. all evaluable pasireotide trough concentrations and UFC levels at matching time points) up to Month 12 for patients who were controlled or partially controlled at Month 6.

While the first analysis based on all patients suggests a flat exposure-response for 600 and 900 µg b.i.d., the latter analysis (based on sub-groups by response status at Month 6) suggests

a trend that higher pasireotide trough concentrations are associated with lower UFC levels in controlled and partially controlled patients. However, because of high inter-patient variability in pasireotide trough concentrations, there is significant overlap in the exposures achieved for the two doses, and the probability of achieving normalization of UFC is comparable for the 600 µg b.i.d. and 900 µg b.i.d. doses.

Exposure-response relationship between pasireotide trough concentrations and probability of UFC normalization at Month 3 using logistic regression model

A logistic regression analysis using Month 3 data of B2305 showed a flat exposure-response relationship between pasireotide trough concentrations and the probability of UFC normalization at Month 3 after adjusting for baseline UFC (Figure 13-10). Furthermore, a repeated-measures model where baseline UFC was averaged over the 2 dose groups showed similar reductions in UFC for both dose groups over time (Figure 13-11). Further details of these analyses are presented in Appendix IV in Section 13. The lack of apparent relationship at Month 3 between pasireotide trough concentrations and probability of UFC normalization may be due to the heterogeneity of the population (i.e. pooled Month 3 data from all patients regardless of their Month 6 response status), and a large inter-patient variability in baseline UFC levels (Table 7-2).

Exposure-response relationship between pasireotide trough concentrations and UFC levels across Months 1-12 for controlled and partially controlled patients using E_{max} model

This analysis included all evaluable pasireotide trough concentrations and UFC values at matching time points collected over the entire 12-month core phase of B2305, including concentrations and UFC levels at all incident dose levels. Because in individual controlled and partially controlled patients UFC levels and pasireotide trough levels tended to correlate, and because a trend towards plateau at the lower end of UFC levels was observed, an inhibitory effect E_{max} model was employed to characterize exposure-response relationship between pasireotide trough concentrations and UFC levels in these patients. The results from E_{max} modeling showed that controlled and partially controlled patients had similar EC_{50} [2.56 ± 2.75 ng/mL vs 2.57 ± 2.58 ng/mL] and similar maximum % UFC reduction [93.5 ± 8.0% vs 90.2 ± 15.7%], suggesting that the pharmacological potency of pasireotide was similar for controlled and partially controlled patients. The $C_{effective}$ was 7.70 ± 8.34 ng/mL for controlled patients. It should be noted that the model estimates of EC_{50} and $C_{effective}$ mentioned above had high inter-patient variability with CV% >100%.

6 Overview of clinical development program

6.1 Overview of pasireotide development in various disease states

The clinical development program for pasireotide has focused on endocrine-related pathologies, i.e. Cushing's disease, acromegaly, and GEP/NET tumors. Two formulations of pasireotide have been used in the clinical development program: an immediate release formulation for s.c. injection and a long-acting release (LAR) formulation for intramuscular

injection. A summary of clinical studies conducted using the pasireotide s.c. formulation that were included in the NDA is provided in Table 6-1.

A summary of planned and completed other studies conducted using the pasireotide s.c. and LAR formulations in patients with Cushing's disease and other indications is shown in Table 6-2.

Table 6-1 Overview of clinical studies with pasireotide included in the NDA

Study	Study objective, population	Number of patients	Treatment duration	Dosage of pasireotide s.c.	Type of control/ blinding
Cushing's disease					
B2305	Double-blind randomized study of 2 dose levels in patients with Cushing's disease to assess efficacy, safety, QoL, PK and PK/PD relationship	162	Core phase 12 months, Extension dependent on clinical benefit	Pasireotide 300 µg b.i.d. 600 µg b.i.d. 900 µg b.i.d. 1200 µg b.i.d.	None/ double-blind
B2208	Open-label, non-randomized study in patients with Cushing's disease to assess efficacy, safety and PK	39	15 days	Pasireotide 300 µg b.i.d. 600 µg b.i.d.	None
B2208E	Open-label extension to assess long-term safety, efficacy and PK	19	Dependent on clinical benefit	Pasireotide 600 µg b.i.d. 900 µg b.i.d.	None
Acromegaly					
B2103	Double-blind randomized 3-way crossover to compare the efficacy of single doses of pasireotide and octreotide	12	Single doses with 6 day washout	Octreotide100 µg pasireotide 100 µg and 250 µg	Active/ double-blind
B2201	Open-label, randomized, crossover study in acromegaly patients to assess efficacy (biochemical response, tumor volume, symptoms), safety, PK/PD relationship	60	16 weeks	Octreotide 100 µg tid for 28 days followed by pasireotide 200, 400, and 600 µg b.i.d. for 28 days each.	None
B2201E	Open-label extension to assess long-term safety, efficacy and PK	30	Dependent on clinical benefit	Pasireotide same as core, with option of dose increase to 900 µg b.i.d.	None
Carcinoid syndrome					
B2202	Open-label, non-randomized study in patients with inadequately controlled carcinoid syndrome to assess efficacy (symptoms, tumor size), safety, QoL and PK	45	Dependent on clinical benefit	Pasireotide 300 µg b.i.d. 600 µg b.i.d. 900 µg b.i.d. 1200 µg b.i.d.	None
Studies B2305, B2208E and B2201E are ongoing					

Table 6-2 Overview of other studies with pasireotide in Cushing's disease and other indications

Study code/status	Study population	Pasireotide formulation and doses	Study design
B2219 (planned; post-approval commitment to EMA)	Cushing's disease (n=planned 25)	Pasireotide 600 µg b.i.d.	Phase IIb, multi-center, open-label, 24-week study to evaluate the effect of proactive, intensive hyperglycemia management
B2410 (planned, FPFV Oct-2012)	Cushing's disease (n=planned 100)	Pasireotide 600 µg and 900 µg b.i.d.	Cushing's disease registry. Non-interventional multinational, multi-center post-marketing study,
B2406 (Enrollment ongoing)	Cushing's disease (n=planned 300)	EU: pasireotide 600 µg b.i.d., increase to 900 µg after 8 weeks if UFC >ULN Other countries: 900 µg b.i.d. or 600 µg b.i.d.	Phase IIIb, open-label, multi-center, expanded access study
G2304 (Enrollment ongoing)	Cushing's disease (n=planned 148)	Pasireotide LAR 10 mg or 30 mg for 4 months, increase to 30 mg or 40 mg if UFC >ULN	Phase III, randomized study of pasireotide LAR 10 mg and 30 mg (i.m. injection every 28 days); double-blind treatment for first 7 months; partial-blind treatment for subsequent 5 months, followed by optional partial-blind extension
C2110 (Completed)	Acromegaly (n=40), carcinoid disease (n=45)	Pasireotide LAR 20, 40 and 60 mg	Phase I, multicenter, open-label, randomized study of pasireotide i.m. injection every 28 days for 3 months, with the option to continue treatment for patients who receive clinical benefit
C2110E (extension to C2110) (ongoing)	Acromegaly (n=29), carcinoid disease (n=31)	Pasireotide LAR 20, 40 or 60 mg; dose could be adjusted by 20 mg at any time (range 20 mg to 60 mg)	Open-label, non-randomized extension to C2110. Patients who completed 3 months of treatment in the first extension phase could enter the second extension phase
C2303 (terminated)	Metastatic carcinoid disease (n= 110)	Pasireotide LAR 60 mg or octreotide LAR 40 mg	Phase III, randomized, blinded efficacy and safety study of pasireotide LAR vs. octreotide LAR (i.m. injection every 28 days)
C2305 Enrollment completed; analyses ongoing	Acromegaly (n=176 pasireotide, 182 octreotide)	Pasireotide LAR 40 mg or octreotide LAR 20 mg; dose escalation to 60 mg/30 mg for patients who do not achieve control of GH and IGF-1	Phase III, randomized, blinded efficacy and safety study of pasireotide LAR vs. octreotide LAR (i.m. injection every 28 days)

6.2 Cushing's disease

6.2.1 Clinical studies in Cushing's disease

Efficacy data are primarily available from the Phase III study B2305, which is the largest study conducted to date in patients with persistent/recurrent Cushing's disease. In addition, results from study B2208 provide proof-of-concept for treatment of patients with Cushing's

disease. Long-term extensions of B2305 and B2208E provide additional data for the long-term safety and efficacy of pasireotide in patients with Cushing's disease.

- Study B2305 was a randomized, multi-center, double-blind Phase III study that evaluated efficacy and safety of 2 doses of pasireotide s.c. (600 µg b.i.d. and 900 µg b.i.d.) in 162 patients with Cushing's disease. The duration of the core study was 12 months, followed by an optional extension phase.
- Study B2208 was a multicenter, open-label, single-arm, proof-of-concept study that assessed safety and efficacy of pasireotide 600 µg b.i.d. s.c. for 15 days in 29 patients with Cushing's disease.
- Study B2208E was an extension to Study B2208, allowing patients who gained significant clinical benefit from treatment in the core study to continue with pasireotide therapy.

None of these studies are placebo or active controlled due to ethical considerations and the unavailability of an appropriate active comparator.

6.2.2 Summary of dose selection in Cushing's disease

The choice of the pasireotide s.c. dose for the first study of pasireotide in patients with Cushing's disease (Study B2208) was based upon information from earlier studies in healthy volunteers (studies B2101, B2102 and B2106) and pasireotide's in vitro SSTR5 binding affinity (Table 2-1).

In healthy volunteers, pasireotide s.c. was well tolerated at the highest tested dose levels, i.e. 1200 µg single dose (study B2101), 1500 µg single dose and split dose (750 µg with 2 injections for a day; study B2106), and 600 µg daily (study B2102). Based on the B2102 dataset, PK simulation predicted that the peak and trough levels of pasireotide s.c. 600 µg b.i.d. at steady state would be approximately 16 ng/mL and 2 ng/mL, respectively, assuming that PK exposures in Cushing's disease patients were similar to those in healthy volunteers.

This trough concentration of ~2 ng/mL was considered to be the minimum concentration for pasireotide to exert its activity toward SSTR5, the postulated target receptor in Cushing's disease. Pasireotide has a binding affinity with IC_{50} value of approximately 0.2 nM (i.e. 0.21 ng/mL; Table 2-1) to SSTR5, which is equivalent to ~1.8 ng/mL in plasma after correction for the free drug fraction in plasma (12% free based on 88% protein binding). As such, maintaining a trough plasma concentration at ~2 ng/mL or above might be necessary for a long term pharmacological activity for pasireotide s.c. Therefore, the dose of 600 µg b.i.d. was selected in Study B2208.

Study B2208 served as a proof-of-concept, Phase II study for the 600 µg b.i.d. dose in patients with Cushing's disease. This study showed that pasireotide 600 µg b.i.d was well tolerated and demonstrated evidence of efficacy. Normalization of UFC was achieved in 5 out of 29 patients (17%) following 15 days of 600 µg b.i.d. treatment. At the end of study on day 15, PK exposures were found as C_{min} 4.9 ± 2.6 ng/mL, C_{max} 21.3 ± 6.9 ng/mL, and $AUC_{0\text{-}8hr}$ 99.7 ± 33.8 ng/mL, respectively, for patients at 600 µg b.i.d. Exposure analysis showed higher PK exposures for UFC responders (UFC normalized) than UFC reducers (UFC decreased from baseline but did not normalize) and UFC non-reducers (UFC ≥ baseline), suggesting a PK/PD relationship between pasireotide exposure and UFC response (Table 6-3). In addition, in the extension B2208E, 1of 4 UFC responders at Month 6 had a dose increase to 900 µg b.i.d. This

led to the selection of a higher dose for the extension part of study B2208 and Phase III study B2305. At 900 µg b.i.d., the average C_{min} was predicted to be 7.35 ng/mL based on a linear dose-exposure relationship for pasireotide (the average C_{min} at 600 µg b.i.d. was 4.9 ng/mL). This predicted value (7.35 ng/mL) was comparable to the average C_{min} observed for UFC responders (7.26 ng/mL; Table 6-3), justifying the inclusion of 900 µg b.i.d. for study B2305. In addition, the 1200 µg b.i.d. dose was included in B2305 as a dose escalation option if no response was achieved after 3 months treatment of 900 µg b.i.d.

Based on these findings, 600 µg b.i.d. and 900 µg b.i.d. were selected as the randomized doses for the Phase III study B2305 in patients with Cushing's disease. In addition, study design of B2305 allowed dose increase to 900 µg b.i.d. at the 600 µg b.i.d. arm, and increase to 1200 µg b.i.d. at the 900 µg b.i.d. arm for patients with lack of response. The study design also allowed dose decrease to 300 µg b.i.d. in the 600 µg b.i.d. arm, and to 600 µg b.i.d. (or further down to 300 µg b.i.d. if needed) in the 900 µg b.i.d. arm for patients with tolerability problems. Taken together, the selection of 600 µg b.i.d. and 900 µg b.i.d. as randomized doses, and the option for dose increase and decrease in both randomized arms, would help dose optimization for individual patients in clinical practice.

Table 6-3 Pasireotide PK parameters by UFC clinical response status on day 15 in patients with Cushing's disease (B2208)

PK Parameter	UFC Responders n=5 mean ± SD (median)	UFC Reducers n=17 mean ± SD (median)	UFC Non-reducers n=4 mean ± SD (median)
C_{min} (ng/mL)	7.26 ± 3.47 (6.06)	4.65 ± 2.49 (3.76)	3.19 ± 1.20 (2.73)
C_{max} (ng/mL)	20.8 ± 4.4 (20.8)	21.8 ± 8.7 (20.4)	17.7 ± 5.3 (16.7)
$AUC_{0\text{-}8hr}$ (hr*ng/mL)	119 ± 33 (116)	99.6 ± 40.8 (88.1)	81.1 ± 25.9 (75.2)

7 Overview of efficacy in Cushing's disease

7.1 Pivotal Phase III study B2305

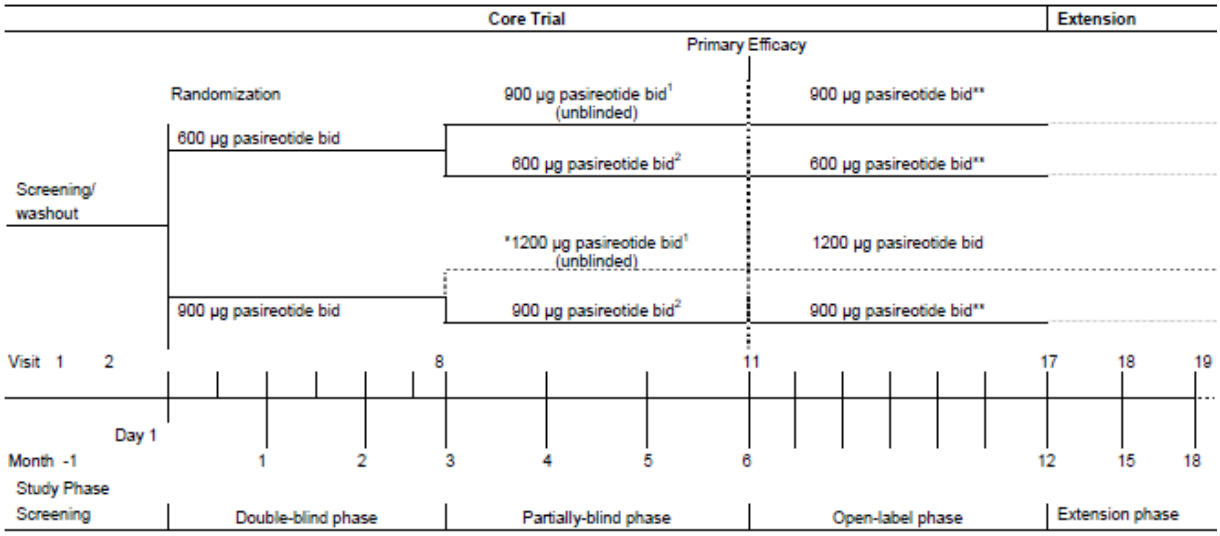
7.1.1 Phase III study design

Study B2305 was a randomized, double-blind Phase III study that evaluated safety and efficacy of 2 doses of pasireotide s.c. in 162 patients with persistent/recurrent Cushing's disease post-pituitary resection or de novo Cushing's disease who were not candidates for surgery.

The design of B2305 is shown in Figure 7-1. Patients were randomized in a 1:1 ratio at baseline to receive pasireotide either 600 µg b.i.d. or 900 µg b.i.d. At Month 3, patients continued at this dose until Month 6 (double-blind treatment) if their Month 3 UFC was a) ≤ 2xULN and b) below or equal to their baseline UFC. Patients not meeting these criteria at Month 3 were unblinded and required to increase their dose by 300 µg b.i.d. with a maximum daily dose of 2400 µg; those whose dose was not increased had to be discontinued from the study. To avoid a potential confounding between dose and responder status, patients who had dose-escalation prior to Month 6 were considered non-responders in the primary efficacy analysis, regardless of their UFC levels at Month 6.

After six months of treatment, patients entered an open-label treatment period where they remained on their current dose level provided a response was observed. If the patient did not respond, or the response was not maintained during the open-label treatment period, the dose could be increased by 300 µg b.i.d. to a maximum daily dose of 1200 µg b.i.d. Dose decrease by 300 µg b.i.d. was allowed any time for lack of tolerability. The duration of the core study was 12 months, after which patients could enter an open-ended extension.

Figure 7-1 Design of Phase III study B2305 in patients with Cushing's disease



[1] Patients with baseline UFC ≥ 2xULN and Month 3 UFC >2xULN or baseline UFC < 2xULN and Month 3 UFC > baseline UFC
[2] Patients with baseline UFC ≥ 2xULN and Month 3 UFC ≤ 2xULN or baseline UFC < 2xULN and Month 3 UFC ≤ baseline UFC
* Permitted dose increase if patient had tolerated 900 µg b.i.d.
** During open-label phase dose could be increased by 300 µg at any time if response was lost
All doses could be reduced by 300 µg at any time for tolerability
China only: doses higher than 900 µg b.i.d. were not allowed

The use of placebo as a comparator was not deemed to be ethical given the morbidity associated with extended states of hypercortisolism and other clinical symptoms associated with this disease. The inclusion of an active comparator in the Phase III study was precluded for several reasons:

- At the time the study was designed there was no approved medical therapy for the treatment of Cushing's disease. There was also no broadly accepted single agent or combination therapy regimen among the available, non-approved therapies. The lack of a well-accepted standard is further impacted by differences in regional availability of the compounds. Therefore, the use of a comparator, single or in combination, would not have been feasible.
- The alternative of including a "best standard-of-care" or "investigator's choice" arm was also considered not feasible due to the complex dose titration schemes required for most alternatives. This not only precludes blinding of the study medication but also poses difficulties to define a common period for efficacy evaluation.

- Blinding would also have been precluded in any of the above options due to the significant DDIs and side effects associated with any of the alternatives. For example, ketoconazole is a potent inhibitor of CYP3A4 and is associated with liver toxicity.

Therefore, the choice of 2 doses of pasireotide s.c. was considered to be appropriate to provide active treatment to both arms, to provide a range of pasireotide doses and to establish efficacy of pasireotide. A potential statistical comparison between the two study arms was precluded due to the relatively higher sample size required.

7.1.2 Key inclusion and exclusion criteria

The eligibility criteria were designed to ensure enrollment of patients with Cushing's disease who were appropriate candidates for medical treatment. Biochemical and clinical confirmation of disease was based on established standard criteria from published guidelines on the differential diagnosis of Cushing's disease (Arnaldi et al 2003). Additionally, specific exclusion criteria for hypercortisolism due to causes other than an ACTH pituitary adenoma were established.

Key inclusion criteria

- Male or female patients aged ≥ 18 years
- Confirmed diagnosis of ACTH-dependent Cushing's disease
- Baseline UFC ≥ 1.5×ULN
- Previous pituitary surgery (confirmation of ACTH-staining adenoma by histopathology required) OR de novo Cushing's disease for patients who were not candidates for pituitary surgery due to surgery being contraindicated, surgically unapproachable tumor, or refusal of surgery
- Adequate washout of prior medical therapy

Key exclusion criteria

- Pituitary irradiation within the last 10 years
- Mitotane within the last 6 months
- Compression of the optic chiasm
- Poorly controlled diabetes mellitus (HbA1c > 8%)
- Risk factors for QTc prolongation and torsade de pointes
- Patients with significant liver disease or with ALT/AST >2xULN or total bilirubin >2xULN

7.1.3 Efficacy evaluation and efficacy criteria

The high morbidity and mortality associated with Cushing's disease is caused by the excessive secretion of cortisol. Consequently, a well-established goal of therapy is to reduce circulating cortisol levels with the ultimate goal of achieving normalization (Biller et al 2008).

UFC was chosen to assess the primary efficacy endpoint as it is directly related to the amount of cortisol that circulates in the blood, provided renal function is adequate. The advantage of

the 24-hour UFC test is that it gives an integrated measure of the free (unbound) cortisol over a 24-hour time period and is thus not sensitive to circadian variation in cortisol levels. It is also not affected by factors that influence corticosteroid-binding globulin levels (Arnaldi et al 2003).

In addition to UFC levels, other important parameters indicative of disease activity and/or clinical benefit were assessed as secondary endpoints. These included hormonal parameters (plasma ACTH, serum cortisol, and salivary cortisol) and a wide array of clinical signs of hypocortisolism (BP, BMI, waist circumference, lipid levels, facial rubor, supraclavicular and dorsal fat pads, hirsutism, striae, proximal muscle strength, bone mineral density and body composition). Pituitary tumor volume was assessed by MRI. Patients' emotional well-being was assessed using the Cushing's disease-specific CushingQOL questionnaire for Cushing's disease-specific HRQL, and the Beck depression inventory II instrument (BDI-II, fourth edition (DSM-IV)).

Further details on the units and scales for evaluating clinical signs and symptoms of Cushing's disease are provided in Appendix I in Section 13.

To minimize bias, photographs used to assess symptoms of hypercortisolism (e.g. facial plethora, fat pads, striae, bruising and hirsutism) were evaluated by a qualified physician who was blinded to treatment and timepoint. MRI images were evaluated centrally by two independent radiologists who were blinded to treatment.

Efficacy parameters

The primary efficacy endpoint in study B2305 was the proportion of responders in each of the pasireotide dose groups at Month 6. A responder was defined as a patient with Month 6 UFC ≤ ULN and no dose increase (relative to the randomized dose) prior to Month 6. Missing Month 6 UFC was imputed using the last available UFC (based on at least 3 samples) between Month 3 and Month 6; if a patient's Month 6 value could not be imputed the patient was considered a non-responder.

The evaluations were based on the 24-hour urinary-free cortisol test (24h-UFC). At the most relevant study time points (e.g. baseline and Months 3, 6 and 12), the mean of four 24-hour UFC collections was used to minimize the inherent variability of this biological marker. For the other time points, where UFC was evaluated, the mean of two 24-hour UFC collections was used. To minimize assay variation all UFC samples were analyzed in a central laboratory. The urine samples were checked for volume and creatinine. Urine cortisol concentrations were measured using high-performance liquid chromatography (HPLC), which has a higher specificity and sensitivity than immunoassays.

Evaluation of the primary efficacy endpoint at Month 6 was chosen in agreement with the FDA as adequate for the efficacy evaluation of a compound intended for chronic treatment. Sustainability of response was further evaluated by inclusion of an additional treatment period of 6 months, thereby bringing the total duration of the core study to 12 months.

In study B2305 the responder rates were tested based on a pre-specified responder analysis, where the minimal response rate of 15% for the lower bound of the 95% CI was considered clinically relevant as spontaneous normalization of UFC is very rare in Cushing's disease (Taylor et al 2003). This was discussed and endorsed by both an external Cushing’s disease

Advisory Board and the study B2305 Study Steering Committee. Both committees considered a response of 15% as clinically meaningful in this disease setting, given the lack of approved medications and more importantly the lack of medications that can be used long-term with demonstrated efficacy and safety.

In the primary efficacy analysis, if the lower bound of the 95% CI for a dose group was greater than 15% then that dose group was considered to have a significant benefit in terms of UFC reduction.

Supportive analyses of the primary efficacy endpoint: additional **clinical response subgroups** based on UFC were defined as follows:

- **Controlled:** Month 6 UFC ≤ ULN (regardless of dose increase).
- **Partially controlled:** Month 6 UFC >ULN but UFC decreased by at least 50% from baseline, regardless of dose increase. The choice of 50% was chosen based on an estimate of the variability of a single sample. This was estimated via the within-patient co-efficient of variation to be 52%. Thus a 50% reduction from baseline was reasonably considered as an indication of intervention effect (Petersenn et al 2010).
- **Uncontrolled:** neither controlled nor partially controlled at Month 6**.**

Per protocol, 4 UFC samples (i.e. 24-hour urine collections) were to be collected over a 2-week period for the Month 6 assessment. If fewer than 3 samples were available the UFC evaluation was considered missing. Unlike the primary efficacy analysis, dose increase was not a factor in this analysis.

Secondary efficacy analyses included proportion of patients with response defined as UFC ≤ ULN at time points up to Month 12, plasma ACTH, serum and salivary cortisol levels, clinical signs and symptoms of Cushing's disease, pituitary tumor volume, Cushing's disease specific HRQL (CushingQOL) score, and the Beck depression inventory score. The proportions of patients satisfying clinically relevant thresholds for BP, BMI, waist circumference and weight were calculated along with the 95% CIs at Months 3, 6 and 12; other parameters were analyzed by descriptive statistics only.

Exploratory efficacy analyses included analysis of response by baseline UFC category and clinical response status over time

Post-hoc efficacy analyses explored the relationship between UFC and clinical signs and symptoms of Cushing's disease (e.g. BMI, weight, high density lipoprotein (HDL), low density lipoprotein (LDL), total cholesterol, triglycerides, systolic and diastolic BP, and CushingQOL scores).

In addition, changes in clinical signs and symptoms were summarized separately for the early uncontrolled patients (uncontrolled at both Month 1 and 2) and the early controlled/partially controlled (Month 1 or 2) patients. A last observation carried forward (LOCF) analysis was also performed to account for the disparity in the discontinuation rates of the two groups (early uncontrolled patients versus early controlled/partially controlled patients).

Analysis sets

The **Full Analysis Set (FAS)** was defined according to the ITT principle and consisted of all randomized patients who received at least one dose of pasireotide. Following the ITT principle, patients were analyzed according to the treatment they were assigned to at randomization. The FAS was used for baseline characteristics, patient disposition and all efficacy analyses.

The **Safety Analysis Set** included all randomized patients who received at least one dose of pasireotide and was used for all safety analyses. The Safety set was identical to the FAS.

The study targeted 73 patients in each arm to deliver 87% power to detect a response rate of 30% in each arm. A dose was considered effective if the lower bound of the 95% CI $\geq$ 15%. The CI was based on normal approximation.

The study was not designed or powered to compare the 2 treatment arms.

Analysis of primary efficacy endpoint

The primary efficacy endpoint of study B2305 was the proportion of patients in each randomized dose group (600 µg b.i.d. and 900 µg b.i.d.) with a decrease in UFC to $\leq$ ULN at Month 6 and whose dose had not been increased relative to the randomized dose prior to Month 6. A dose was considered to be effective if the lower bound of the 95% CI of the response rate was greater than the pre-specified null hypothesis of 15%.

Patients who discontinued before Month 3 evaluation were considered non-responders in the primary efficacy analysis. If Month 6 UFC was missing then it was imputed by the last available UFC (of at least 3 samples) between (and including) Month 3 and Month 6. Patients without such assessments between Months 3 and 6 were considered non-responders.

Analysis of Quality of Life

A single-domain, 12-item Cushing's disease-specific HRQL questionnaire (CushingQOL) was implemented in this study (Webb et al 2008). Summary scores, obtained as a direct sum of all 12 item response scores, were calculated and standardized to a 0-100 scale at each assessment. Lower scores indicate worse Cushing's disease-related HRQL.

Patients who completed at least 9 items (75% or more of the total items) at an assessment were considered evaluable for that visit. The count and proportion of patients who had sufficient information available for analysis were tabulated at baseline, Months 3, 6, and 12 (or final study visit) by dose groups and overall. Standardized scores and their changes from baseline were descriptively summarized and plotted at each assessment by treatment arm.

Further details on the CushingQOL questionnaire are provided in Appendix I (Section 13).

7.2 Baseline characteristics and patient disposition in B2305

Study B2305 enrolled patients at 68 sites in 18 countries across 4 continents (North and South America, Europe and Asia). Of 329 screened patients, 162 patients were enrolled between Dec-2006 and Mar-2009. At the time of the data cut-off used for the NDA submission (17-Mar-2010), all patients had completed the 12-month core phase of the study (or discontinued

early). At the time of the most recent data cut-off used for the safety update (30-Dec-2011), patients who entered the extension had received at least 33 months (i.e. 33x28 days) of treatment across the core and extension phases, or discontinued.

7.2.1 Baseline demographics and disease characteristics

Patient demographics and disease characteristics were as expected in a population where the majority had persistent or recurrent Cushing's disease post-pituitary resection. The mean age was approximately 40 years, with fewer than 5% overall aged 65 or over. Women accounted for three quarters of all patients.

The majority of patients had a baseline UFC that was several times above the ULN of 145 nmol/24h, therefore, their disease status was moderate to severe in nature. The overall baseline mean UFC of 970 nmol/24hr was 6.7xULN; 84% of all patients had UFC >2xULN, and 38% had UFC >5xULN. In line with the severity of disease are the observations that patients on average had high BP (mean 133.5/86.3 mmHg), were obese (mean BMI 30.3 kg/m^2, mean waist circumference 103.1 cm), and had elevated total cholesterol (mean 5.8 mmol/L).

Baseline disease characteristics were comparable between the 2 dose groups, with the exception of baseline mean UFC levels which were higher in the 600 µg b.i.d. group than in the 900 µg b.i.d. group (mean±SD 1155.9 ± 2629.78 and 781.2 ± 926.38 nmol/24h, respectively; note that patients were not stratified by baseline UFC).

Table 7-1 Baseline demographics (B2305)

	Pasireotide 600 µg b.i.d. N=82	Pasireotide 900 µg b.i.d. N=80	Overall N = 162
Age (years)			
n	82	80	162
Mean±SD	40.5±12.97	39.9±10.77	40.2±11.90
Median	39.0	41.0	39.0
Min-Max	18-67	19-71	18-71
Age - n (%)			
< 65 years	78 (95.1)	79 (98.8)	157 (96.9)
≥ 65 years	4 (4.9)	1 (1.3)	5 (3.1)
Sex - n (%)			
Male	20 (24.4)	16 (20.0)	36 (22.2)
Female	62 (75.6)	64 (80.0)	126 (77.8)
Race - n (%)			
Caucasian	65 (79.3)	62 (77.5)	127 (78.4)
Black	2 (2.4)	1 (1.3)	3 (1.9)
Asian	10 (12.2)	10 (12.5)	20 (12.3)
Native American	2 (2.4)	2 (2.5)	4 (2.5)
Other	3 (3.7)	4 (5.0)	7 (4.3)
Missing	0	1 (1.3)	1 (0.6)
Ethnicity - n (%)			
Hispanic/Latino	29 (35.4)	22 (27.5)	51 (31.5)
Chinese	10 (12.2)	10 (12.5)	20 (12.3)
Mixed ethnicity	0	1 (1.3)	1 (0.6)
Other	43 (52.4)	46 (57.5)	89 (54.9)
Missing	0	1 (1.3)	1 (0.6)

Table 7-2 Baseline disease characteristics and history (B2305)

		Pasireotide 600 µg b.i.d. N=82	Pasireotide 900 µg b.i.d. N=80	Overall N=162
Time (months) to first pasireotide dose since diagnosis				
N		82	80	162
Mean (SD)		53.38 (63.79)	54.70 (62.79)	54.03 (63.11)
Median		35.48	29.70	33.99
Min –Max		0.10-341.78	0.10-372.14	0.10-372.14
Cushing's Disease Status – n (%)	De novo	15 (18.3)	12 (15.0)	27 (16.7)
	Persistent/recurrent	67 (81.7)	68 (85.0)	135 (83.3)
Any previous surgery – n (%)	No	18 (22.0)	16 (20.0)	34 (21.0)
	Yes	64 (78.0)	64 (80.0)	128 (79.0)
Any previous pituitary irradiation – n (%)	No	79 (96.3)	76 (95.0)	155 (95.7)
	Yes	3 (3.7)	4 (5.0)	7 (4.3)
Any previous medication – n (%)	No	46 (56.1)	38 (47.5)	84 (51.9)
	Yes	36 (43.9)	42 (52.5)	78 (48.1)
Baseline UFC (nmol/24h)				
N		77	76	153
Mean (SD)		1155.94 (2629.779)	781.90 (926.384)	970.14 (1979.020)
Median		730	487	564.5
Min-Max		219.50-22943.75	195.00-6122.75	195.00-22943.75

Time to first pasireotide dose since diagnosis = (First pasireotide dose date – date of diagnosis of Cushing's disease +1)*12/365.25.

Table 7-3 Baseline blood pressure, weight, waist circumference, BMI and total cholesterol (B2305)

	Pasireotide 600 µg b.i.d. N=82		Pasireotide 900 µg b.i.d. N=80	
	n	Mean (SD)	**n**	Mean (SD)
Blood pressure (mmHg)*				
Systolic	82	132.0 (18.70)	80	135.0 (20.17)
Diastolic	82	85.7 (12.90)	80	87.0 (12.33)
Weight (kg)	82	81.9 (22.43)	80	81.3 (20.64)
Waist circumference (cm)	79	103.3 (18.32)	79	102.8 (17.73)
BMI (kg/m^2)	82	30.4 (7.01)	80	30.2 (7.07)
Total cholesterol (mmol/L)	82	5.9 (1.29)	80	5.7 (1.35)

*Sitting blood pressure

7.2.2 Patient disposition

Of the 165 patients that were randomized into this study, 3 did not receive study drug (Table 7-4). These 3 patients were screening failures, but the investigators had chosen the IVRS randomization option by mistake. Of the 162 patients who were correctly randomized into the study, all received at least one dose of pasireotide. A total of 78 patients (48.1%) completed Month 12 (end of core study). The proportion of patients who completed Month 12 was similar in both dose groups.

Of the 78 patients who completed the core phase, 58 patients entered the optional extension, and 20 patients chose not to continue (reasons for not participating in the extension were not collected). Note that in the original analysis it was reported that 57 patients entered the extension. Since that data cut-off (17-Mar-2010) one additional patient (from the 600 µg b.i.d. group) was counted as having entered the extension. The 58th patient was not considered to have entered the extension at the time of the Month 12 analysis as the patient's extension visits were not entered in the database at that time. The proportion of patients who entered the extension was slightly higher in the 900 µg b.i.d. group (40.0%) than in the 600 µg b.i.d. group (31.7%).

A total of 97 patients (59.9%) discontinued the study (core or extension) at any time up to data cut-off. Patients could discontinue from the study due to unsatisfactory therapeutic effect, tolerability issues, withdrawal of consent, or protocol deviation. A patient could be discontinued for lack of efficacy if, after 3 months of treatment on the maximal dose of pasireotide, UFC was $\geq$ 2xULN or in the investigator's opinion the efficacy was not satisfactory. Unsatisfactory therapeutic effect was the most frequent reason for discontinuation (25.3% of patients), followed by AEs (17.3%) and withdrawal of consent (14.8%). The rates of discontinuation, and the reasons for discontinuation, were similar between the dose groups.

For discussion of discontinuation reasons over time see Section 8.1.1.

Table 7-4 Patient disposition (B2305)

Disposition Reason	Pasireotide 600 µg b.i.d. N=83 n (%)	Pasireotide 900 µg b.i.d. N=82 n (%)	Overall N = 165 n (%)
Randomized	83 (100.0)	82 (100.0)	165 (100.0)
Randomized but not treated	1 (1.2)	2 (2.4)	3 (1.8)
Randomized and treated	**82 (98.8)**	**80 (97.6)**	**162 (98.2)**
Completed Month 6	54 (65.9)	53 (66.3)	107 (66.0)
Completed Month 12	**39 (47.6)**	**39 (48.8)**	**78 (48.1)**
Discontinued at any time*	49 (59.8)	48 (60.0)	97 (59.9)
Reason for discontinuation			
Unsatisfactory therapeutic effect	19 (23.2)	22 (27.5)	41 (25.3)
Adverse event(s)	13 (15.9)	15 (18.8)	28 (17.3)
Subject withdrew consent	13 (15.9)	11 (13.8)	24 (14.8)
Protocol deviation	4 (4.9)	0	4 (2.5)
Discontinued at or prior to Month 6	28 (34.1)	27 (33.8)	55 (34.0)
Discontinued prior to Month 12 but after Month 6	15 (18.3)	14 (17.5)	29 (17.9)
Completed Month 12 and Entered Extension Phase	**25 (30.5)**	**32 (40.0)**	**57 (35.2)**
Completed Month 12 and did not enter Extension phase*	14 (17.1)	7 (8.8)	21 (13.0)
Discontinued study in Extension phase	6 (7.3)	7 (8.8)	13 (8.0)
Ongoing in Extension phase*	**19 (23.2)**	**25 (31.3)**	**44 (27.2)**

Note: % for the first three rows based on N. % for the remaining rows based on randomized and treated subjects.
*Patients who completed Month 12 and did not enter extension phase are not counted as discontinuations.
Ongoing at the cut-off date (17-Mar-2010)

7.3 Efficacy in B2305

7.3.1 Biochemical efficacy

7.3.1.1 Primary efficacy endpoint – UFC response at Month 6

The primary efficacy endpoint in study B2305 was the proportion of patients who achieved normalization of UFC in each of the pasireotide dose groups at Month 6. Patients with a dose increase (relative to the randomized dose) prior to Month 6 were considered non-responders in this analysis.

The results of the primary efficacy analysis in study B2305 are shown in Table 7-5. The 900 µg b.i.d. dose group met the primary efficacy endpoint, with a response rate of 26.3% at Month 6 (95% CI 16.6 to 35.9; the lower bound of the 95% CI was greater than the pre-specified null hypothesis of 15%). The 600 µg b.i.d. group did not meet the primary efficacy endpoint as the response rate was 14.6% (95% CI 7.0 to 22.3). However, the 600 µg b.i.d. dose was also shown to be efficacious, as discussed below.

Table 7-5 Primary efficacy analysis – proportion of responders at Month 6 (B2305)

	Pasireotide 600 µg b.i.d. N=82	Pasireotide 900 µg b.i.d. N=80	Overall N=162
Response - n (%)	12 (14.6)	21 (26.3)	33 (20.4)
95% Confidence Interval	(7.0, 22.3)	(16.6, 35.9)	(14.2, 26.6)

95% Confidence Intervals are based on normal approximation to the binomial distribution.

Missing Month 6 values were imputed with assessment at Month 3 or later for 2 patients in each group.

Three patients (1 in the 600 µg b.i.d. and 2 in the 900 µg b.i.d. groups) were considered non-responders because they had a dose increase prior to Month 6.

7.3.1.2 Proportion of patients with UFC <= ULN over time

The proportion of patients with UFC ≤ ULN in each dose group up to Month 12 is graphically displayed in Figure 7-2. In this analysis no imputation of missing values was used.

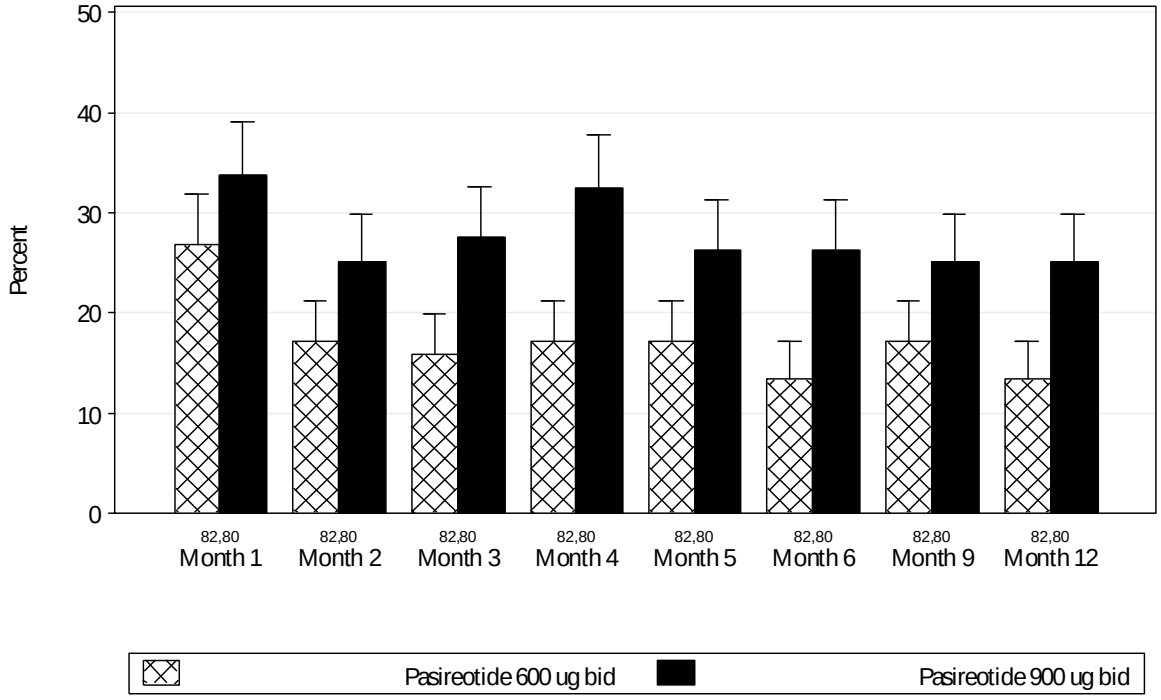
The proportion of patients with UFC ≤ ULN was higher in the 900 µg b.i.d. group than in the 600 µg b.i.d. group at all time points up to Month 12.

At Month 1, 26.8% (95% CI 17.2 to 36.4) and 33.8% (95% CI 23.4 to 44.1) of patients in the 600 and 900 µg b.i.d. groups, respectively, had UFC ≤ ULN. This is noteworthy given the higher baseline mean UFC levels in the 600 µg b.i.d. group relative to the 900 µg b.i.d. group (see Table 7-2).

At Month 6, 13.4% (95% CI 6.0 to 20.8) and 26.3% (95% CI 16.6 to 35.9) of patients in the respective groups had UFC ≤ ULN. These results, in which no imputation of missing data was used and where a patient's dose increase does not play a role, is consistent with the response rate observed in the primary efficacy analysis shown in Table 7-5.

At Month 12, the results were consistent with those at Month 6, with 13.4% (95% CI 6.0 to 20.8) and 25.0% (95% CI 15.5 to 34.5) of patients in the 600 and 900 µg b.i.d. groups, respectively, having UFC ≤ ULN.

Figure 7-2 Proportion of patients with UFC <= ULN at time points up to Month 12 (B2305)



+1 standard error is displayed on each bar. The numbers 80, 82 below the bars are the denominators used to calculate the percentages and represent the FAS.

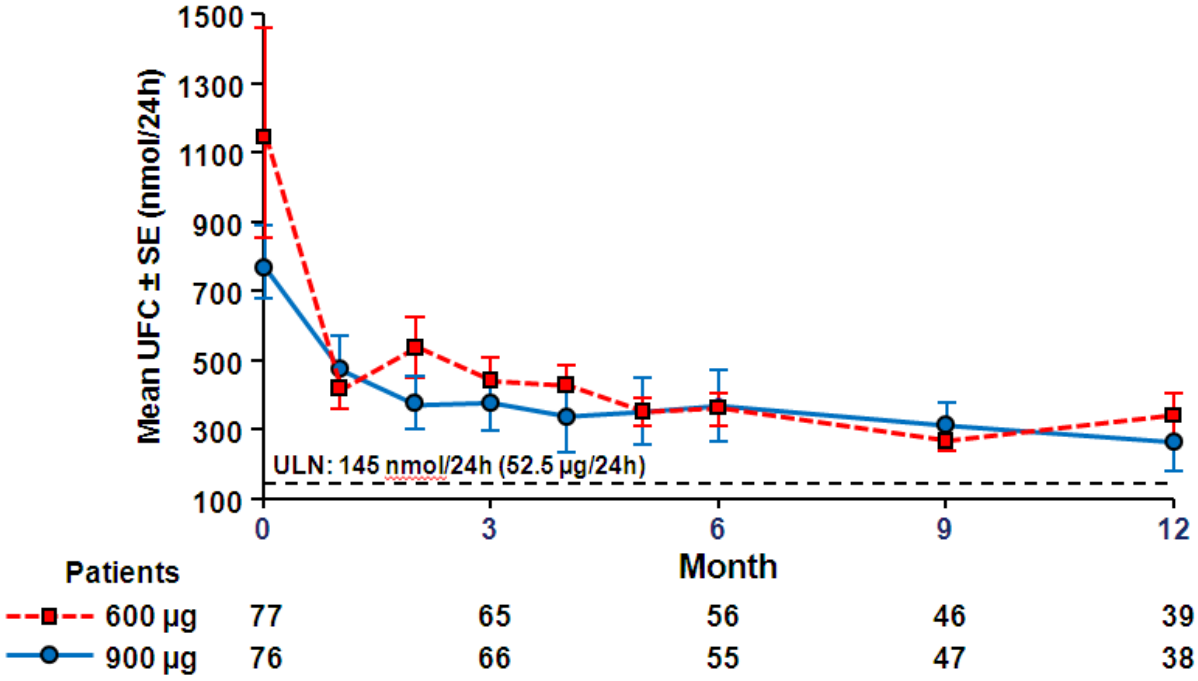
7.3.1.3 UFC levels over time

As shown in Figure 7-3, mean UFC levels decreased markedly in both dose groups within the first month of treatment. The decrease in UFC was sustained over time and is considered clinically meaningful. The mean absolute change from baseline to Month 6 was numerically greater in the 600 µg b.i.d. group (-463.4 nmol/24h) than the 900 µg b.i.d. group (-364.9 nmol/24h) . The median % reduction in UFC was similar in both randomized groups, despite the higher baseline UFC in the 600 µg b.i.d. group (47.9%; Table 13-2).

Figure 7-3 also highlights the higher baseline mean UFC levels in the 600 µg b.i.d. group relative to the 900 µg b.i.d. group (1155.9 ± 2629.78 vs. 781.9 ± 926.38 nmol/24h). Note that despite the higher baseline mean UFC level in the 600 µg b.i.d. group, mean UFC levels decreased to comparable levels at Month 6.

The relationship between baseline UFC and UFC response at Month 6 is discussed further in Section 7.3.1.5.

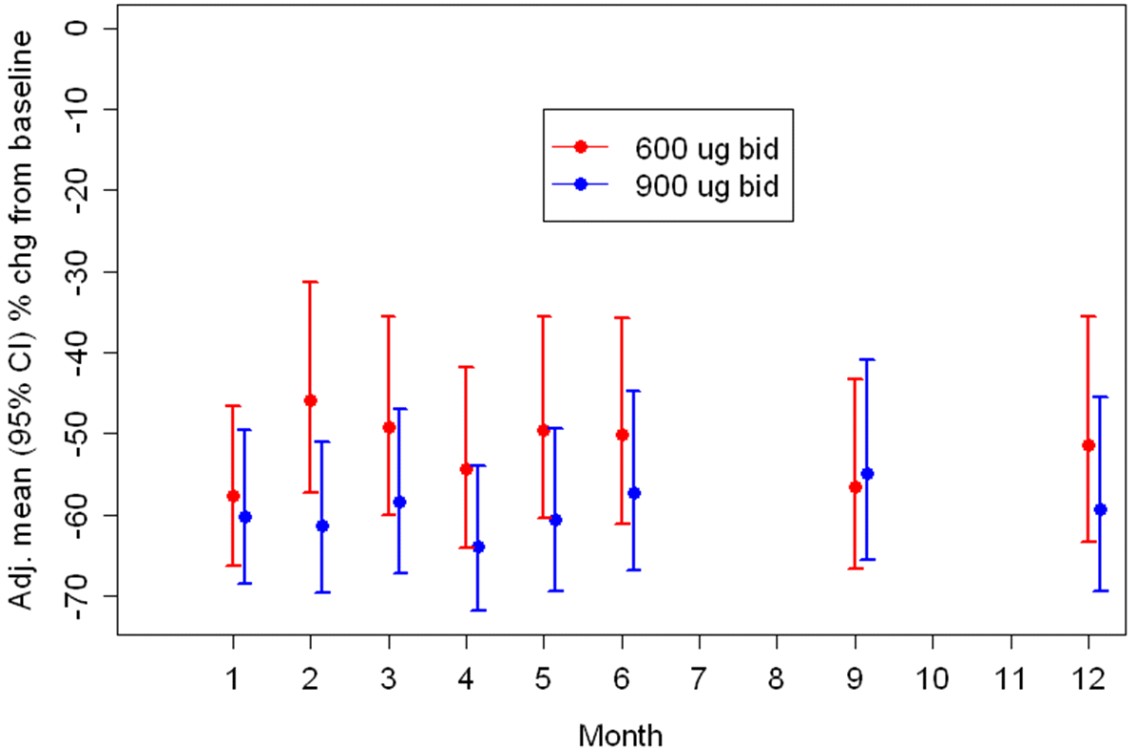
Figure 7-3 UFC levels up to Month 12 (B2305)



A minimum of 3 UFC samples were required at Months 0 (baseline), 3, 6 and 12, and a minimum of 2 UFC samples were required at other time points; otherwise a patient's UFC assessment at that time point was considered missing.

The longitudinal UFC data up to Month 12 were also analyzed using a repeated measures model to assess the robustness of the observed reduction in UFC in the 2 dose groups to the imbalance in baseline UFC between the dose groups, and to missing values. As shown in Figure 7-4, the adjusted mean percent change in UFC from baseline to Month 1 was greater than 50% in both dose groups, and was between 40 and 60% at subsequent time points. These results are consistent with those shown in Figure 7-3.

Figure 7-4 **Adjusted mean % change in UFC levels from baseline using a repeated measures model up to Month 12 (B2305)**



7.3.1.4 Other efficacy endpoints related to UFC levels

Clinical response subgroups at Month 6 and Month 12 independent of dose increase

The proportion of patients who were controlled, partially controlled, and uncontrolled at Month 6 and at Month 12 is summarized in Table 7-6.

In the 600 µg b.i.d. group, 15.9% of patients were controlled, and 18.3% were partially controlled at Month 6. In the 900 µg b.i.d. group, 28.8% and 12.5% of patients were controlled and partially controlled, respectively. The results were similar at Month 12, apart from a lower proportion of partially controlled patients in the 900 µg b.i.d. group. At Month 6, the proportion of patients who were controlled or partially controlled was 34.1% in the 600 µg b.i.d. group and 41.3% in the 900 µg b.i.d. group; at Month 12, the results were 29.3% and 27.5% for the 600 and 900 µg b.i.d. groups, respectively.

Table 7-6 Clinical response subgroups at Month 6 and Month 12 (B2305)

	Pasireotide 600 µg b.i.d. N=82	Pasireotide 900 µg b.i.d. N=80	Overall N=162
Month 6			
Controlled or partially controlled – n (%)	**28 (34.1)**	**33 (41.3)**	**61 (37.7)**
Controlled – n (%)	13 (15.9)	23 (28.8)	36 (22.2)
Partially controlled – n (%)	15 (18.3)	10 (12.5)	25 (15.4)
Month 12			
Controlled or partially controlled – n (%)	**24 (29.3)**	**22 (27.5)**	**46 (28.4)**
Controlled – n (%)	11 (13.4)	20 (25.0)	31 (19.1)
Partially controlled – n (%)	13 (15.9)	2 (2.5)	15 (9.3)

Controlled responders: UFC ≤ ULN (regardless of dose increase).

Partially controlled responders: UFC >ULN but had at least 50% decrease from baseline, regardless of dose increase.

Missing Month 6 UFC was imputed for a total of 8 patients (2 controlled patients in each dose group and 2 partially controlled patients in each dose group).

Dose change and UFC response

The dose could be increased (by 300 µg b.i.d.) at the Month 3 visit if the patient's UFC >2x ULN or if mUFC was higher than baseline, and after 6 months if the patient's UFC >ULN.

Prior to Month 6, the dose of pasireotide was increased in 36 patients (24 and 12 patients in the 600 and 900 µg b.i.d. groups, respectively). At Month 6, 1 patient with a dose increase from 600 µg b.i.d. to 900 µg b.i.d. and 2 patients with a dose increase from 900 µg b.i.d. to 1200 µg b.i.d. achieved control. In terms of partial control, the results showed that 8 of 15 patients in the 600 µg b.i.d. group who were partially controlled at Month 6 had a dose increase prior to Month 6; however, in the 900 µg b.i.d. group only 1 of 10 partially controlled responders had a dose increase prior to Month 6.

In patients with dose increase from 600 to 900 µg b.i.d. at Month 3, a slight decrease in mean UFC was observed: from 710.4 nmol/24h at Month 3 (before dose increase) to 571.3 nmol/24h at Month 4 (after dose increase). In contrast, in patients with dose increase from 900 to 1200 µg b.i.d. at Month 3, mean UFC was similar at Month 3 (833.4 nmol/24h) and at Month 4 (908.5 nmol/24h).

A patient's dose could be reduced (by 300 µg b.i.d.) in case of grade 3 or higher drug-related AEs or if there was evidence of hypocortisolism. At Month 6, of the 13 controlled patients randomized to the 600 µg b.i.d. group, 5 patients were receiving a dose of 300 µg b.i.d. Similarly, of the 23 controlled patients who were randomized to the 900 µg b.i.d. 5 patients were receiving a dose of 600 µg b.i.d. For the patients who had a lower dose at the Month 6 visit, the timing of the dose decrease varied, but all were receiving a lower dose for more than 1 month at the time of the Month 6 assessment.

7.3.1.5 Analysis of primary endpoint by baseline UFC categories

As illustrated in Figure 7-3, baseline UFC was higher in the 600 µg b.i.d. group than in the 900 µg b.i.d. group. The higher baseline UFC in the 600 µg b.i.d. group could have adversely

affected the response rate in this group relative to the 900 µg b.i.d. group, as patients with high baseline UFC require a larger decrease in UFC to achieve normalization.

As shown in Table 7-7, the number of patients with severe hypercortisolism at baseline (i.e. UFC >5xULN) was higher in the 600 µg b.i.d. group (39 patients) than the 900 µg b.i.d. group (22 patients). Analysis of the primary efficacy endpoint by baseline UFC shows that the response rate in patients with moderate to severe hypercortisolism (i.e. baseline UFC >2xULN) was similar between the 600 and 900 µg b.i.d. groups, and that in both dose groups the response rates were lower for patients with more severe hypercortisolism (i.e. baseline UFC >5xULN). However, in the 600 µg b.i.d. group, patients with mild hypercortisolism at baseline (i.e. UFC ≤ 2xULN) had a lower response rate (8.3%) than those with more severe hypercortisolism in the same dose group (26.9% among patients with baseline UFC >2xULN to ≤ 5xULN), or in patients with mild hypercortisolism in the 900 µg b.i.d. group (50.0%). The low response among the 12 patients with mild hypercortisolism in the 600 µg b.i.d. is counter-intuitive, and may be due to chance - among these 12 patients, 3 patients had a late response (i.e. normalization of UFC after 6 months), and 1 patient had normal UFC at all visits except the one at Month 6.

Taken together, these results show that the response rates in both dose groups were comparable for patients with moderate to severe hypercortisolism at baseline, and suggest that the higher baseline UFC in the 600 µg b.i.d. group may have had a negative impact on the overall response rate in this group.

Table 7-7 Analysis of primary efficacy endpoint by baseline UFC category (B2305)

Baseline UFC category	Pasireotide 600 µg b.i.d. N=82 n/N (%) (95% CI)	Pasireotide 900 µg b.i.d. N=80 n/N (%) (95% CI)
>ULN to ≤ 2xULN	1/ 12 (8.3) (0.0, 24.0)	7/ 14 (50.0) (23.8, 76.2)
>2xULN to ≤ 5xULN	7/ 26 (26.9) (9.9, 44.0)	10/ 40 (25.0) (11.6, 38.4)
>5xULN to ≤ 10xULN	3/ 28 (10.7) (0.0, 22.2)	1/ 13 (7.7) (0.0, 22.2)
>10xULN	1/ 11 (9.1) (0.0, 26.1)	0/ 9 (0.0) N/A
Missing	0/ 5 (0.0) N/A	3/ 4 (75.0) (32.6, 100.0)
Total	12/82 (14.6) (7.0, 22.3)	21/80 (26.3) (16.6, 35.9)

7.3.1.6 Change from baseline in ACTH and serum cortisol

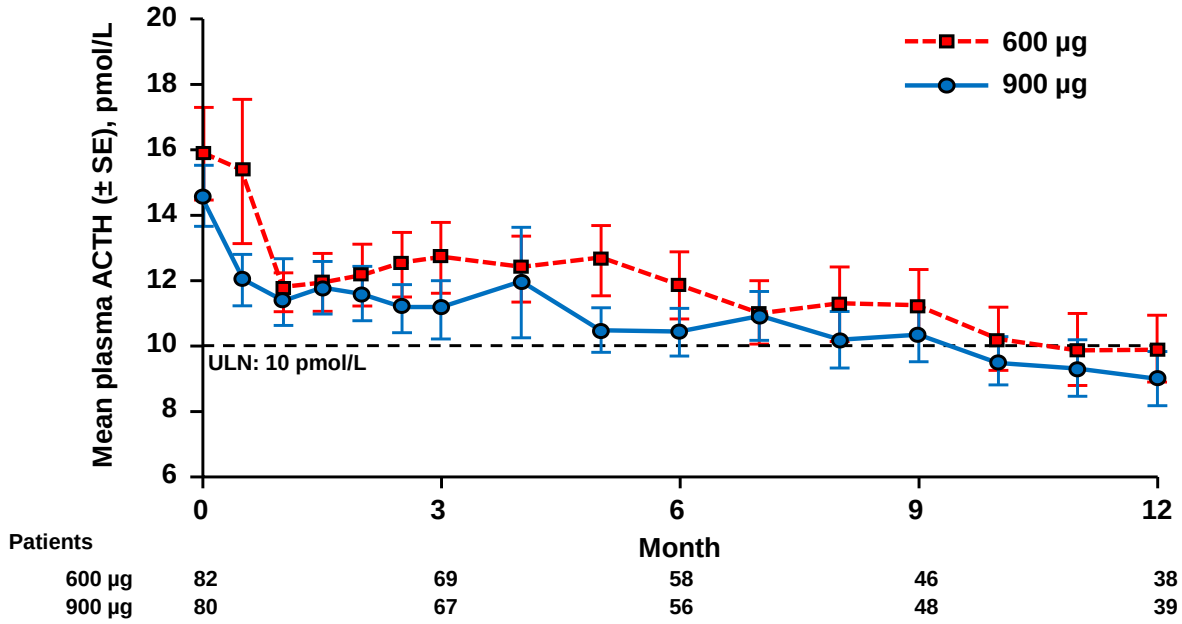
Plasma ACTH

Mean plasma ACTH levels (measured in the morning of each visit) decreased to below baseline by Month 0.5 in the 900 µg b.i.d. group and by Month 1 in the 600 µg b.i.d. group

and remained below baseline levels at all subsequent time points for both dose groups (Figure 7-5). Mean baseline ACTH levels were 15.9 and 14.6 pmol/L in the 600 and 900 µg b.i.d. groups, respectively. At Month 6, mean ACTH had decreased to 11.8 and 10.4 pmol/L, respectively. The improvements were sustained at Month 12, with mean ACTH levels of 9.9 and 9.0 pmol/L in the respective groups.

The decrease in ACTH is particularly important in that it supports the proposed mechanism of action of pasireotide in Cushing's disease and provides evidence of an efficacious pituitary-targeted medical therapy.

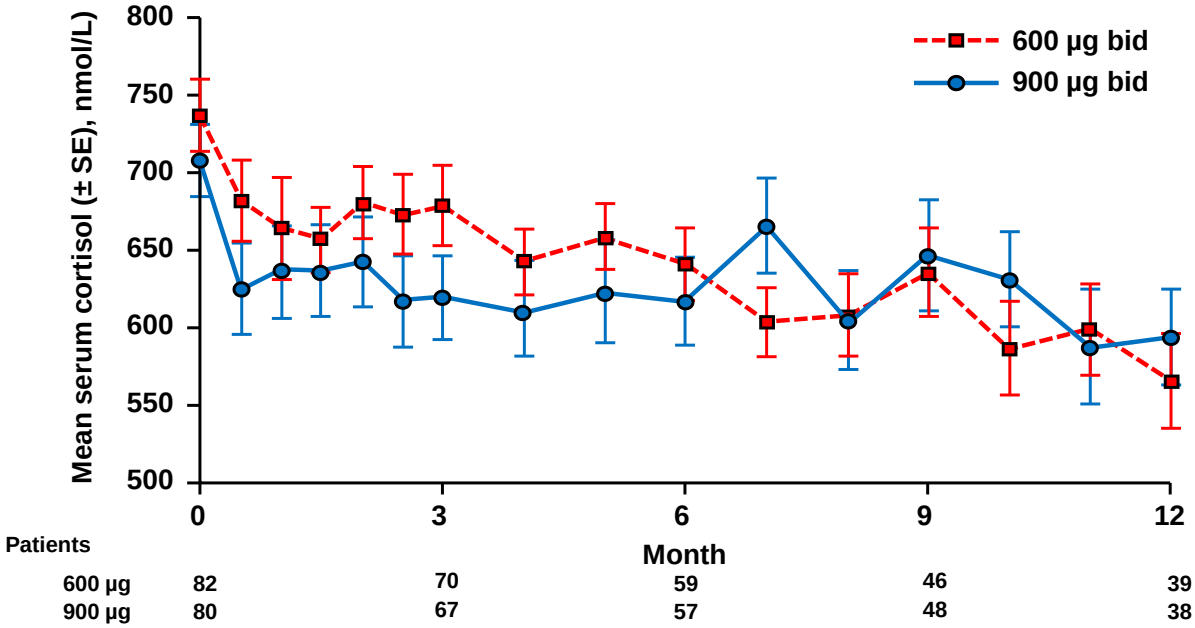
Figure 7-5 Mean (+/-SE) plasma ACTH (pmol/L) levels up to Month 12 (B2305)



Serum cortisol

Mean serum cortisol levels (measured in the morning at each visit) decreased below baseline by Month 0.5 and remained below baseline levels at all subsequent time points for both dose groups (Figure 7-6). Mean baseline cortisol levels were 737.7 and 706.6 nmol/L in the 600 and 900 µg b.i.d. groups, respectively. At Month 6, mean cortisol levels had decreased to 641.0 and 616.9 nmol/L. Similarly to the ACTH levels, the improvements in serum cortisol levels were sustained at Month 12, with mean values of 565.6 and 593.3 nmol/L in the respective groups.

Figure 7-6 Mean (+/- SE) serum cortisol (nmol/L) levels up to Month 12 (B2305)



Midnight salivary cortisol

Measurement of midnight salivary cortisol was introduced as an exploratory analysis during the study. Mean (±SD) baseline salivary cortisol levels were 35.9±82.5 (n=48) and 29.1±82.9 (n=45) nmol/L in the 600 and 900 µg b.i.d. groups, respectively. At Month 6, levels had decreased to 13.1±14.3 (n=41) and 11.0±11.6 (n=33) nmol/L. A slight further decrease was seen at Month 12, with mean values of 11.9±8.8 (n=32) and 10.5±10.4 (n=32) nmol/L in the respective groups.

7.3.2 Clinical efficacy

7.3.2.1 Clinical signs and symptoms of Cushing's disease

As a result of persistent hypercortisolism patients with Cushing's disease are often obese, with characteristic central obesity, are hypertensive, and have elevated blood lipid levels. As discussed in Section 7.2.1, the majority of patients in study B2305 had moderate to severe hypercortisolism (as evidenced by high baseline UFC levels), and high mean BP, BMI, and total cholesterol levels (see also Table 7-3).

In Study B2305, the decrease in UFC seen with pasireotide was paralleled by clinically relevant improvements in BP, BMI, weight and total cholesterol. The relationship between UFC and these parameters over time is illustrated in the figures below: systolic and diastolic BP (Figure 7-7), weight (Figure 7-8), BMI (Figure 7-9), and total cholesterol (Figure 7-10). Additional plots for lipid profile (LDL, HDL and triglycerides) are shown in Appendix II in Section 13. Note that because the reductions in UFC were similar over time in both dose groups, data for both dose groups are combined in these graphs for better clarity.

Changes in these parameters were more pronounced in the higher randomized dose group, as shown in Table 13-4.

Blood pressure

At baseline, 126 patients (77.8%) were hypertensive, defined as a medical history of hypertension, history of antihypertensive medication, or systolic BP >130 mmHg or diastolic BP >90 mmHg. Baseline mean BP in the 600 and 900 µg b.i.d. groups were 132.0/85.7 and 135.0/87.0 mmHg, respectively, as expected for a hypertensive population (Table 7-3). At Month 6, mean BP had decreased to 124.7/82.1 mmHg (mean decrease of 6.8/4.2 mmHg) in the 600 µg b.i.d. group, and to 126.3/83.6 mmHg (mean decrease of 11.4/5.0 mmHg) in the 900 µg b.i.d. group. These improvements were sustained up to Month 12, at which time mean BP was 127.9/84.6 mmHg and 124.2/80.9 mmHg, respectively. The results show that the decrease in BP is more pronounced in the 900 than the 600 µg b.i.d. dose group.

Regardless of randomized dose group, the decrease in BP measured was greatest in patients whose UFC was controlled at Month 6. The overall mean decrease in BP from baseline to Month 6 was 13.4/7.7 mmHg for controlled patients, 7.5/3.4 mmHg in partially controlled patients, and 7.3/3.2 mmHg in uncontrolled patients (both dose groups combined).

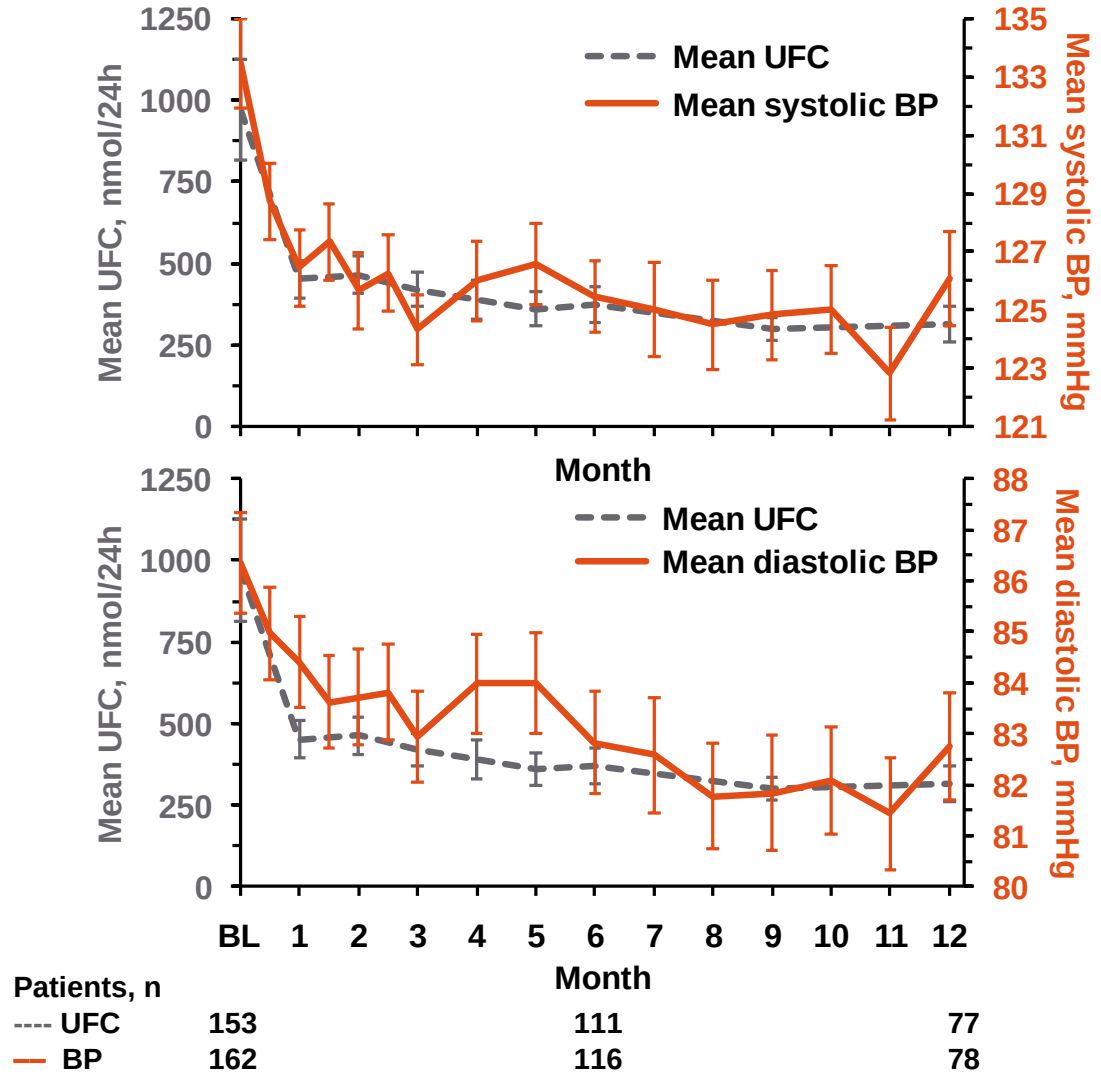
Table 7-8 shows change in BP from baseline to Month 12 analyzed by patients' hypertensive status at baseline. The results showed that BP decreased in hypertensive patients, but not in normotensive patients (mean change in BP was -8.0/-4.7 mmHg in hypertensive patients vs. 0.2/-0.4 mmHg in normotensive patients). Furthermore, in hypertensive patients, the decrease in BP was more pronounced among those who did not use antihypertensive medication during the study (mean decrease 13.2/7.3 mmHg) relative to those who did (mean decrease 6.1/3.7 mmHg). Note that use of medication for hypertension during the study was at the discretion of the investigator.

Table 7-8 Change in BP to Month 12 by baseline hypertensive status (B2305)

	Change in SBP (mmHg) Mean (95% CI)	Change in DBP (mmHg) Mean (95% CI)
Overall, N=78	-6.1 (-9.8, -2.4)	-3.7 (-6.2, -1.2)
Hypertension at baseline	–8.0 (–12.4, –3.6)	–4.7 (–7.7, –1.7)
No antihypertensive medication use during study, n=16	–13.2 (–20.0, –6.4)	–7.3 (–12.9, –1.7)
Antihypertensive medication use during study, n=44	–6.1 (–11.5, –0.7)	–3.7 (–7.2, –0.2)
No hypertension at baseline	0.2 (–6.1, 6.4)	–0.4 (–4.6, 3.9)
No antihypertensive medication use during study, n=13	–0.3 (–8.2, 7.6)	–0.9 (–6.2, 4.5)
Antihypertensive medication use during study, n=5	1.5 (–9.1, 12.1)	1.0 (–6.0, 8.0)

SBP=systolic blood pressure; DBP=diastolic blood pressure

Figure 7-7 **Mean (+/-SE) UFC (nmol/24h) and systolic and diastolic blood pressure (mmHg) up to Month 12 (B2305)**



Weight, BMI, waist circumference

As shown in Table 7-3, baseline mean values for weight, BMI and waist circumference are compatible with a patient population that is overweight or obese with central adiposity. Weight (Figure 7-8), BMI (Figure 7-9) and waist circumference decreased in both dose groups, with decreases being more pronounced in the 900 than the 600 µg b.i.d. group (Table 13-4). At Month 6, the mean decrease from baseline (600 vs. 900 µg b.i.d. group) was as follows: weight 3.1 kg vs. 5.7 kg, BMI 1.2 kg/m^2 vs. 2.1 kg/m^2, and waist circumference 1.9 cm vs. 3.4 cm. Further improvements were seen at Month 12, with mean decreases as follows: weight 5.8 kg vs. 7.7 kg, BMI 2.1 kg/m^2 vs. 2.8 kg/m^2, and waist circumference 4.4 cm vs. 5.6 cm.

Figure 7-8 Mean (+/-SE) UFC (nmol/24h) and weight (kg) up to Month 12 (B2305)

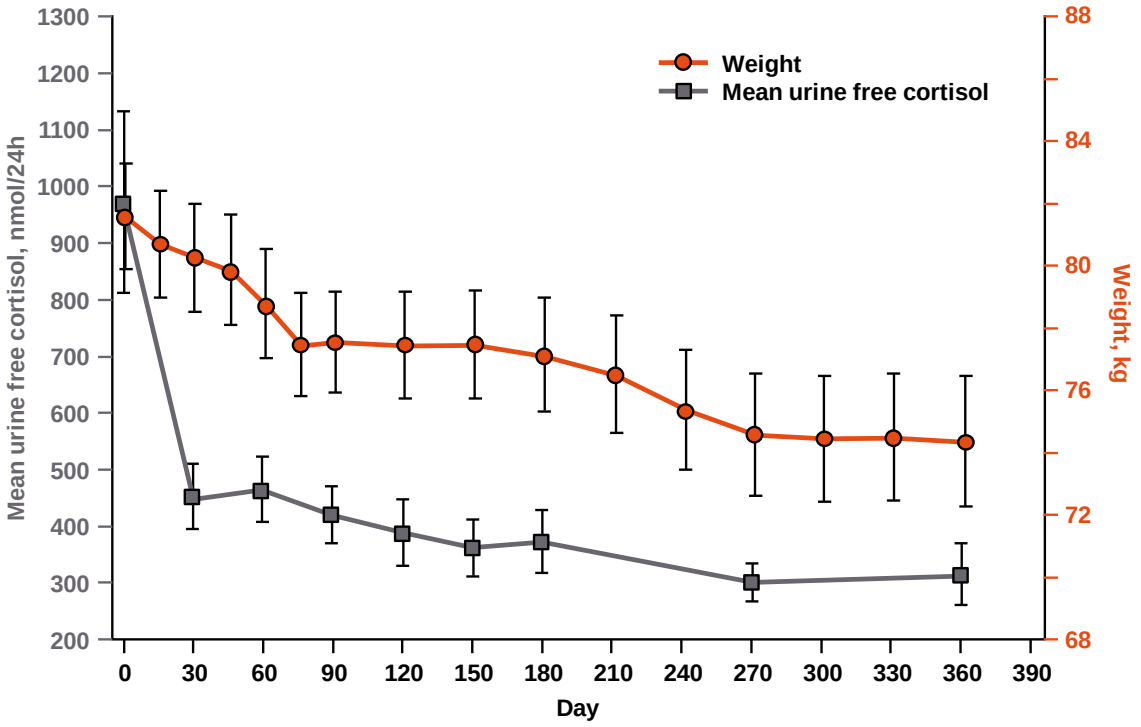
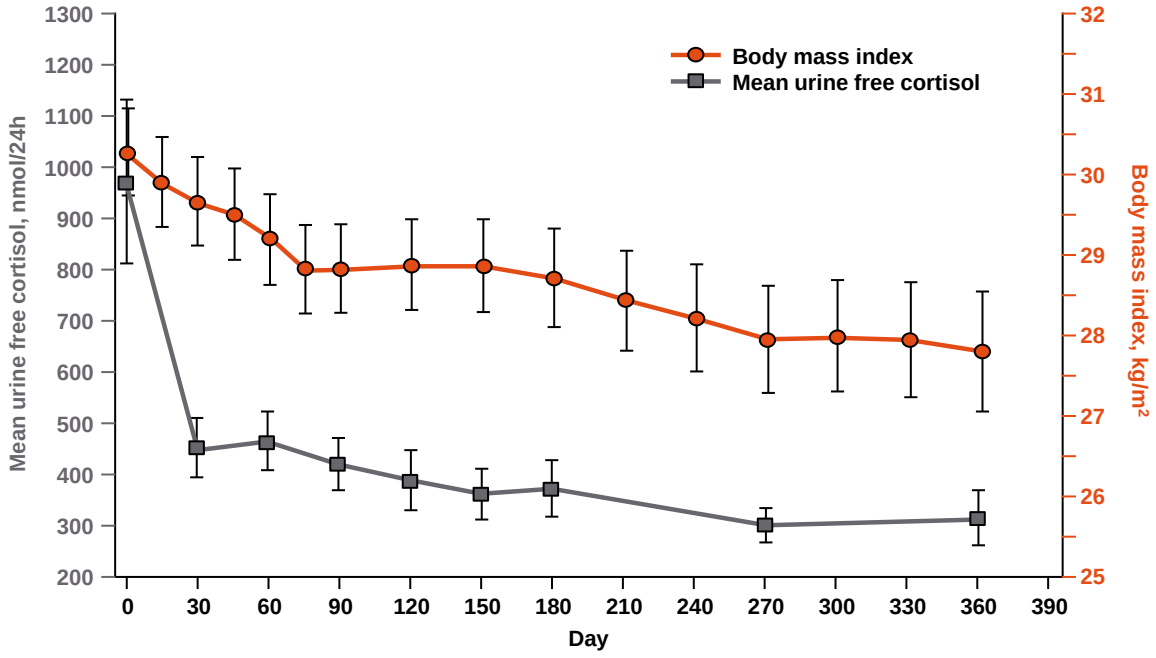


Figure 7-9 Mean (+/-SE) UFC (nmol/24h) and BMI (kg/m^2) up to Month 12 (B2305)

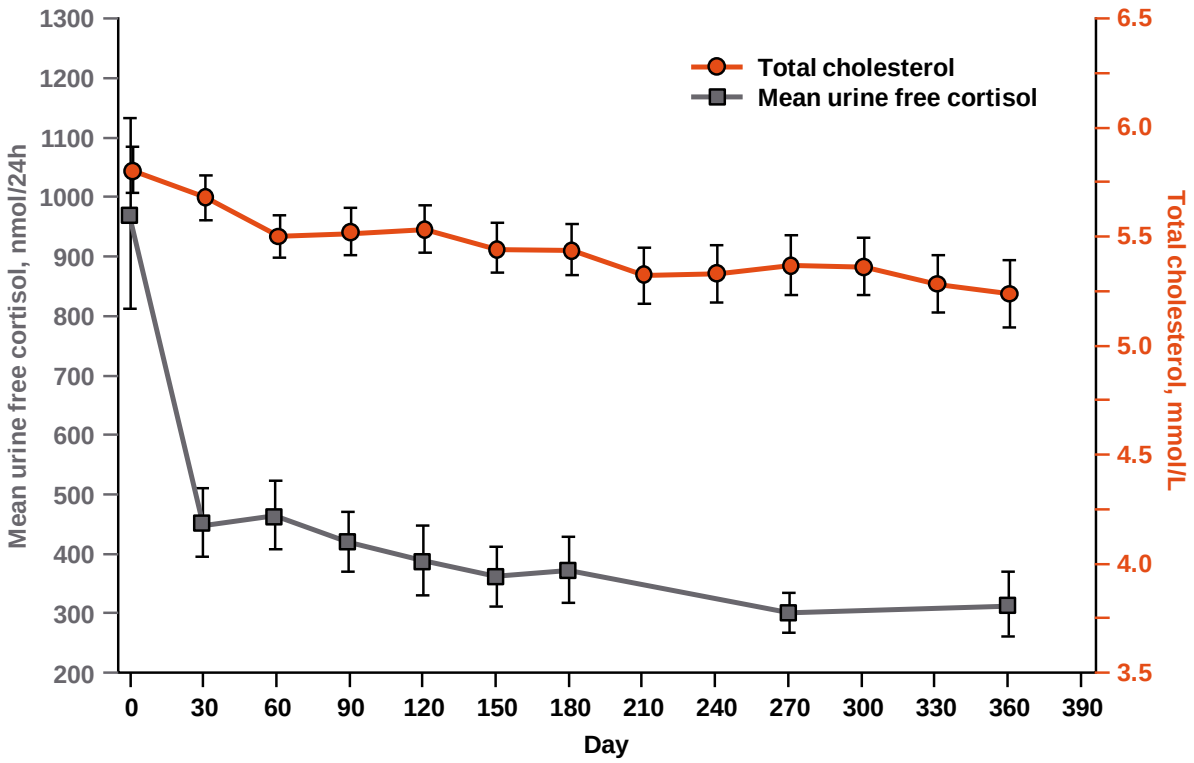


Lipids

Slight decreases were seen over time in total cholesterol, LDL and triglycerides (Figure 7-19, Figure 13-2, Figure 13-3), but not in HDL levels (Figure 13-1). For both dose groups combined, mean total cholesterol levels decreased from 5.8 mmol/L at baseline to 5.4 mmol/L at Month 6 and 5.2 mmol/L at Month 12. Mean LDL levels decreased from 3.5 mmol/L at baseline to 3.2 mmol/L at Month 6 and 3.0 mmol/L at Month 12. Triglyceride levels were 1.8 mmol/L at baseline and at Month 6, and decreased to 1.6 mmol/L at Month 12.

Mean HDL levels were around 1.5 mmol/L at baseline, at Month 6 and at Month 12.

Figure 7-10 Mean (+/-SE) UFC (nmol/24h) and total cholesterol (mmol/L) up to Month 12 (B2305)



Clinical signs and symptoms in responders

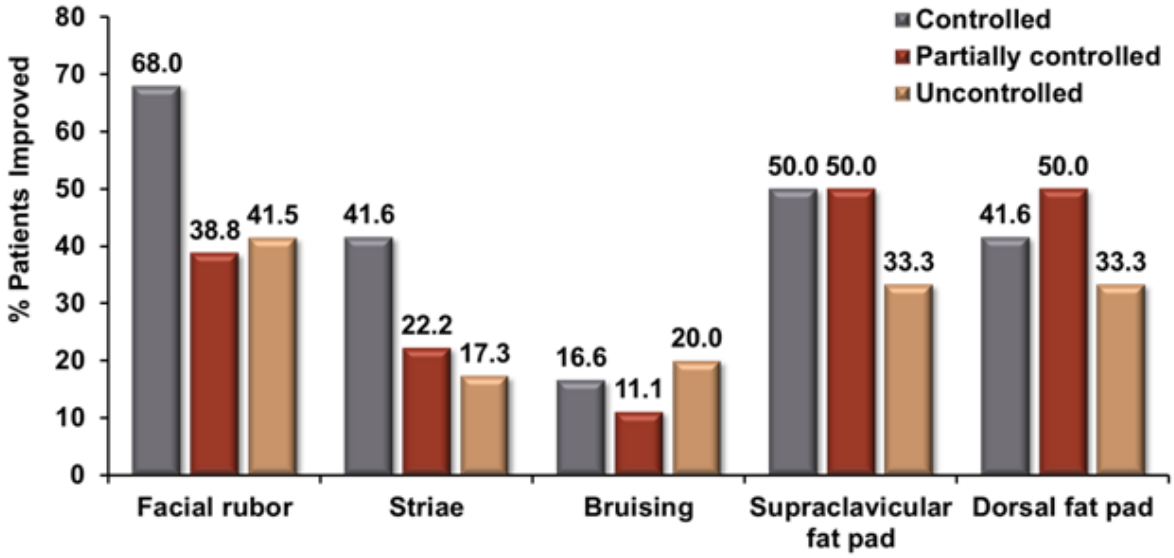
Table 13-4 (Appendix II) shows changes in clinical signs of Cushing's disease at Month 6 by patients' responder status at Month 6. These analyses show that improvements are generally more pronounced in patients who are controlled or partially controlled. However, improvements were also seen in patients whose UFC was not controlled at Month 6, showing that these patients derive clinically relevant benefit from pasireotide treatment.

Physical features by type of UFC response at Month 6

Overall, improvements were observed in all the studied physical signs of Cushing’s disease (i.e. facial rubor, striae, bruising, supraclavicular fat pad, dorsal fat bad, and muscle strength)

in both pasireotide dose groups (for details on assessments see Appendix I in Section 13). As shown in Figure 7-11 for both dose groups combined, approximately half of evaluable patients had less severe symptoms of facial rubor and fat pads (both supraclavicular and dorsal) at Month 6, whereas favorable shift for striae and bruising were also seen. Importantly, many patients had improvements in their symptoms at Month 6, regardless of their response status. These analyses also show that not only patients who are controlled or partially controlled at Month 6 receive clinically relevant benefit from pasireotide treatment, but that also those patients who are uncontrolled at Month 6 had clear benefit.

Figure 7-11 Patients with favorable shift from baseline in physical features of Cushing's disease at Month 6 (B2305)



7.3.2.2 Tumor volume

As shown in Table 13-3 in Appendix II, clinically meaningful decreases in tumor volume measured by MRI were observed with pasireotide treatment, confirming the proposed pituitary-targeted mechanism of pasireotide. The mean decrease from baseline in tumor volume in the 900 µg b.i.d. group was 19.0% (n=28) at Month 6 and 43.8% (n=18) at Month 12. The changes in tumor volume in the 600 µg b.i.d. group were too small to be clinically meaningful. Note that the number of patients with measurable tumor volume at baseline was small, which is as expected considering that the majority of patients (around 80%) had pituitary surgery prior to study entry (Table 7-2).

7.3.3 Health-related quality of life

As shown in Figure 7-12 with data for both dose groups combined, mean CushingQOL scores improved up to Month 12 in parallel with the decrease in mean UFC levels. Improvements in CushingQOL scores were seen at the first assessment time point at Month 3; scores continued to improve up to Month 12, showing that patients perceived an improvement in their quality of life with pasireotide treatment.

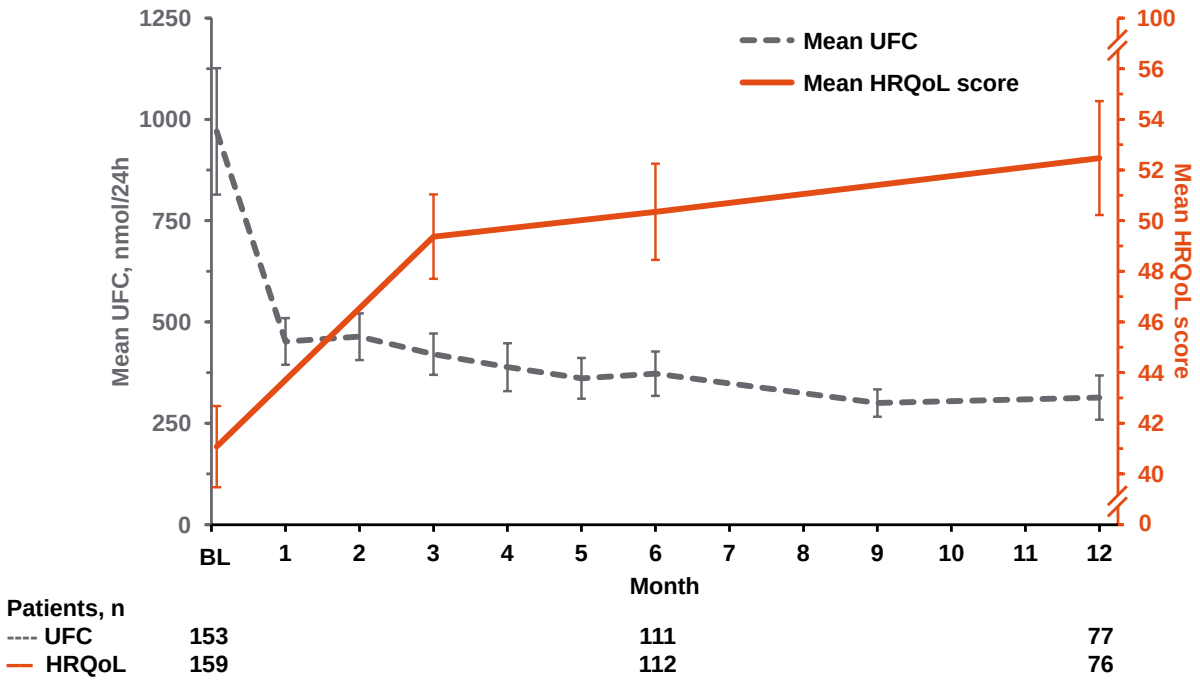
These improvements in CushingQOL scores were seen in both dose groups. At baseline, mean CushingQOL scores were similar for the two dose groups (mean ±SD 41.6±20.41 and 40.5±20.11 in the 600 and 900 µg b.i.d. groups, respectively). The increase in mean scores at Month 6 was numerically greater in the 900 µg b.i.d. group (mean increase 12.9 points) than in the 600 µg b.i.d. group (mean increase 6.2 points). The mean change in the 900 µg b.i.d. group exceeded the threshold for meaningful change in CushingQOL of 10.1 units (for details on defining meaningful change in CushingQOL see Appendix I, Section 13).

At Month 12, the mean CushingQOL scores had increased to 50.0±20.32 (mean increase from baseline 9.4 points) in the 600 µg b.i.d. group and to 54.8±18.87 (mean increase from baseline 12.8 points) in the 900 µg b.i.d. group, showing that patients in both dose groups continued to experience improvement in Cushing's disease-related quality of life with longer pasireotide treatment.

CushingQOL scores were also analyzed by Month 6 UFC response subgroup (both dose groups combined). At Month 6, the mean improvement in CushingQOL scores were comparable for patients whose UFC was controlled, partially controlled or uncontrolled at Month 6 (mean increases of 9.6, 8.9 and 9.7 points, respectively). At Month 12, patients whose UFC was controlled at Month 6 had improved more (mean increase 12.8 points) than those who were partially controlled (mean increase 10.7 points) or uncontrolled (mean increase 9.9 points).

Details on the CushingQOL instrument are provided in Appendix I, Section 13.

Figure 7-12 Mean (+/-SE) UFC (nmol/24h) and CushingQOL up to Month 12 (B2305)



7.4 Supportive studies

7.4.1 Phase II results – study B2208

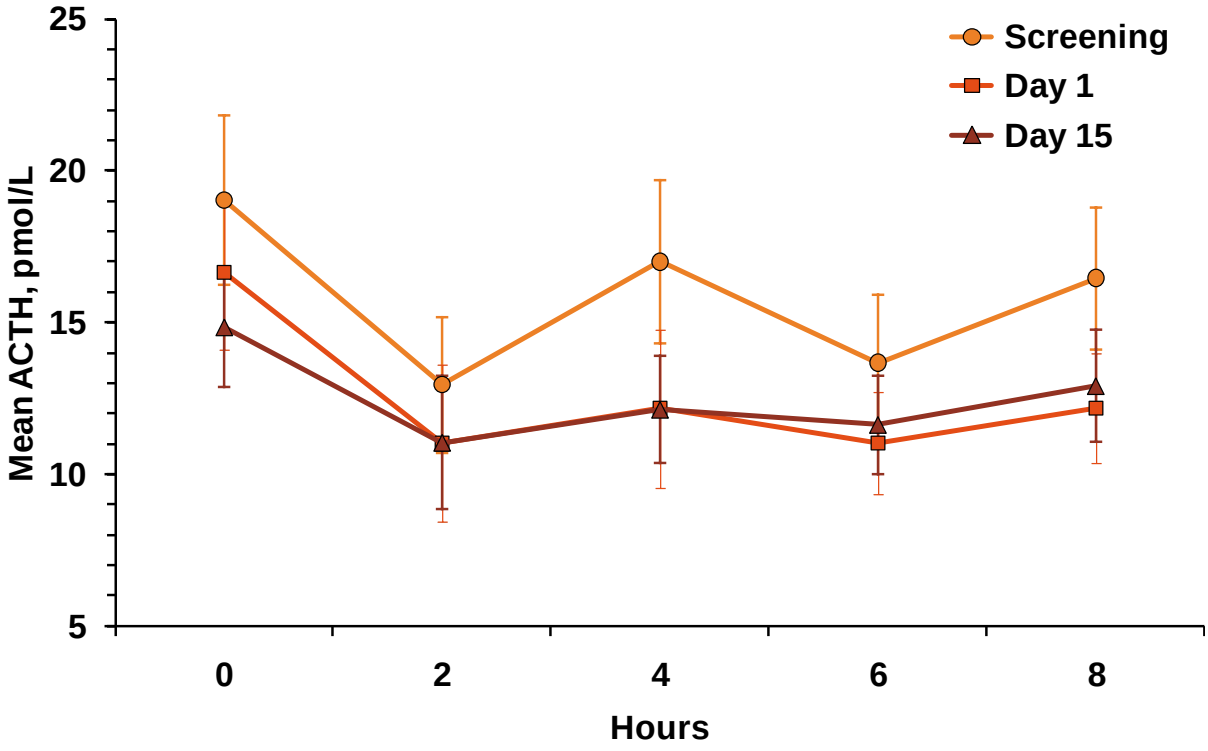
In B2208, a phase II open-label, proof-of-concept study, patients with de novo, persistent or recurrent Cushing's disease were treated with pasireotide 600 µg sc b.i.d. for 15 days. In this short-term study UFC normalized in 5 of 29 patients (17%), the primary endpoint for this study, and 22 patients (76%) had a decrease in UFC compared to baseline. Mean UFC level decreased from 1231 nmol/24 h at baseline to 683 nmol/24 h at day 15 (a reduction of 44.5%).

Decreases in mean serum cortisol and plasma ACTH were also demonstrated (Figure 7-13). With respect to clinical signs and symptoms associated with Cushing's disease, a positive effect (i.e. a slight decrease in BP) was demonstrated in most patients in the core study in spite of the fact that the treatment duration (i.e. 15 days) was potentially not long enough to see a marked effect.

Nineteen patients entered the extension study (B2208E) and 3 patients are currently ongoing, thereby allowing pasireotide treatment to continue for those patients who experienced significant clinical benefit from treatment. Dose escalation up to a maximum dose of 900 µg s.c. b.i.d. is permitted. For the 16 patients that discontinued the primary reasons for discontinuation were to start new therapy (5 patients), unsatisfactory therapeutic effect (3 patients) or withdrawal of consent (3 patients). Two patients discontinued due to abnormal laboratory values, one patient discontinued due to an AE, and for 2 patients a reason was not specified.

Of the 18 patients included in the efficacy analysis, 4 patients (22%) achieved normalization of UFC at 6 months, while a consistent reduction in mean UFC relative to core baseline values was maintained throughout the extension study period. An effect on diastolic BP was also evident. Note: one patient who entered the extension was excluded from the efficacy analysis population due to having normal UFC values at study entry.

Figure 7-13 Effect of pasireotide on mean ACTH (+/-SE) in patients with Cushing's disease (B2208)



7.4.2 Evidence from published data

A single, prospective, open-label, multicenter study (Feelders et al 2010) was conducted in 17 patients with Cushing's disease using pasireotide 100 to 250 µg three times daily as monotherapy, followed by combination therapy (i.e. pasireotide plus cabergoline, or pasireotide plus cabergoline and ketoconazole). Results of this small study further support the efficacy of pasireotide in Cushing's disease: 5 of 17 (29%) patients normalized UFC on pasireotide monotherapy after 27 days. All the patients who normalized UFC on pasireotide monotherapy had baseline UFC values ≤ 2xULN. Additional data on combination therapy are presented in the publication.

Significant differences in patient population (e.g. lower baseline UFC entry criteria and majority of patients' with de novo disease) and study design (e.g. pasireotide dosing regimen, UFC assay and UFC normal ranges) limit any direct comparison between this study and B2305.

7.5 Persistence of efficacy

The extension phase of study B2305 is currently ongoing. Of the 58 patients who entered the optional extension, 21 patients were still ongoing as of 30-Dec-2011, at which time all patients had completed a total of 33 months (i.e. 33 cycles of 28 days) of treatment. The most frequent reasons for discontinuation in the extension were withdrawal of consent (13 patients) and unsatisfactory therapeutic effect (13 patients). Nine patients withdrew due to AEs, one

patient due to abnormal test procedure results, and one patient was lost to follow-up (see Table 13-5 in Appendix II).

The mean duration of exposure overall at the time of the 30-Dec-2011 data cut-off was 15 months. Forty patients had at least 24 months of exposure, and 10 patients had at least 48 months of exposure.

7.5.1 Long-term suppression of UFC

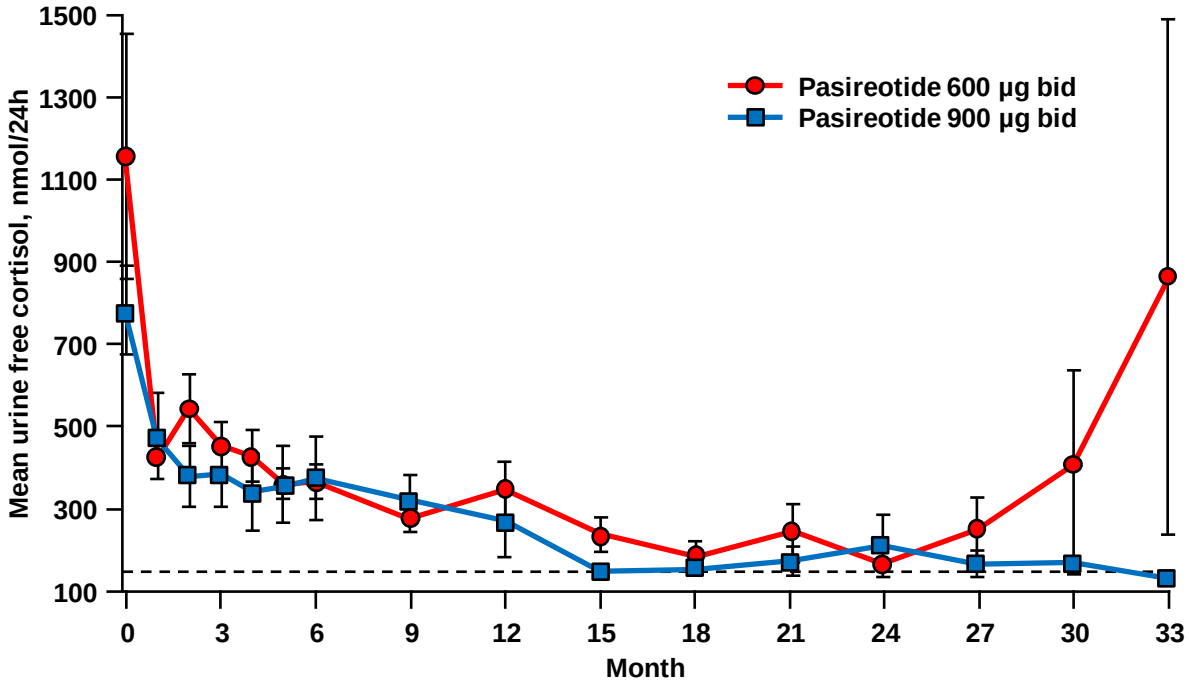
Figure 7-14 shows mean UFC values (±SE) over time for the 600 and 900 µg b.i.d. dose groups up to Month 33. Summary statistics for additional data points are presented in Table 13-6 in Appendix II. The data show that the initial rapid, robust decrease in UFC was sustained with longer follow-up in both dose groups.

As shown in Figure 7-14, in the 900 µg b.i.d. group the mean UFC levels remained close to ULN during the extension phase up to Month 33. In the 600 µg b.i.d. group, mean UFC levels remained close to ULN for the first 2 years of treatment. However at Months 30 and 33 an increase in mean UFC is observed. This increase is due to a heavy influence of a few extreme outlying values on the mean (note that the effect of extreme outliers on the mean becomes stronger at later time points because the number of patients providing data decreased over time (from a total of 153 at the start of treatment to 27 at Month 33), therefore the mean values at later time points have to be interpreted with caution). There were 3 patients in the 600 µg b.i.d. group with extreme outlying UFC values at Month 30 and Month 33; details on these patients are provided further below.

As can be seen of the plot of median UFC values in Figure 7-15, the median remains relatively constant in both dose groups during the extension. In addition, data is available for a few patients who had reached time points beyond Month 33 at the time of the data cut-off of 30-Dec-2011 (see Table 13-6 in Appendix II). The mean UFC among those patients was below ULN during the year following Month 36.

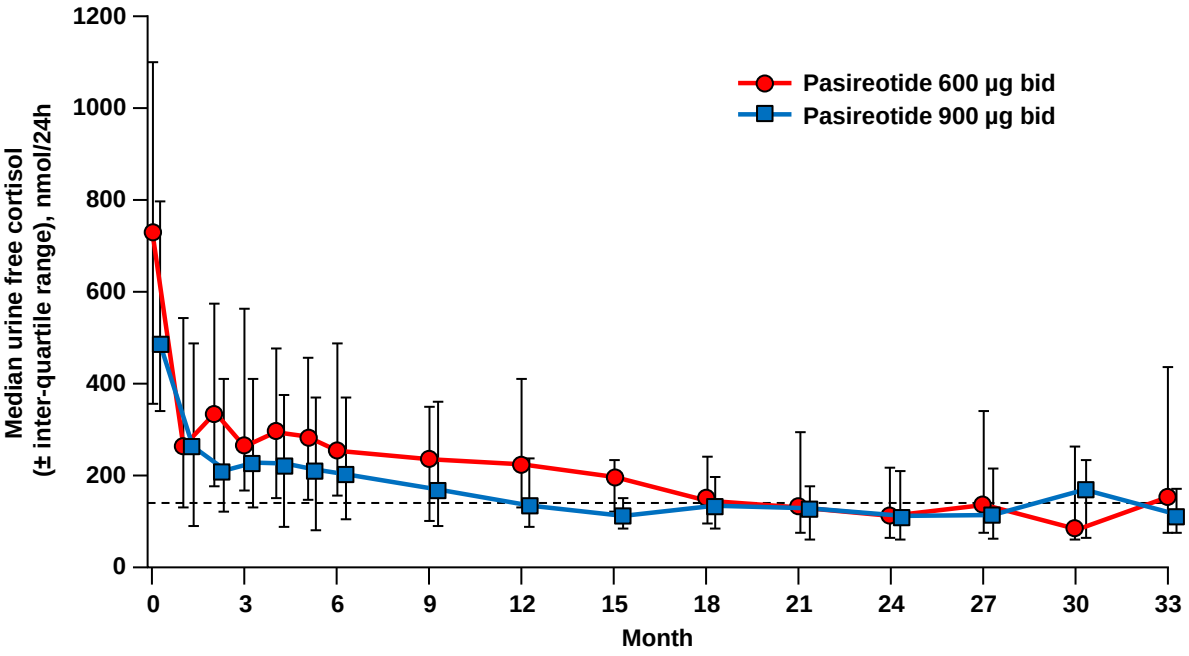
As shown in Figure 7-15, median UFC values remain relatively constant in both dose groups during the extension, confirming that the decrease in UFC was sustained for most patients who continued in the study.

Figure 7-14 Mean (+/-SE) UFC levels up to Month 33 (B2305)



At least three 24h UFC assays contributed to patient mean results at Months 0 (baseline), 3, 6 and 12. At least two 24h UFC assays contributed to patient mean results at other time points.
+/-Standard errors are displayed.
----- is the ULN for the UFC assay (145 nmol/L)

Figure 7-15 Median UFC levels (+/- inter-quartile range) up to Month 33 (B2305)



At least three 24h UFC assays contributed to patient mean results at Months 0 (baseline), 3, 6 and 12. At least two 24h UFC assays contributed to patient mean results at other time points.
----- is the ULN for the UFC assay (145 nmol/L)

Details on the 3 patients in the 600 µg b.i.d. group who had extreme UFC values after the first 2 years of treatment are as follows:

- One patient with baseline UFC of 220 nmol/24h had post-baseline values <100 nmol/24h at most time points up to Month 42, but some elevated values between Month 27 and Month 33 (Month 24, 27, 30, 33 and 36 UFC values were 43, 583, 2699, 833 and 65 nmol/24h, respectively). During this time period the patient had dose interruptions lasting between 2 and 10 days due to AEs (myalgia and abdominal pain). The patient was still ongoing at the time of data cut-off.
- One patient with baseline UFC of 4564 nmol/24h had post-baseline values <400 nmol/24h at most time points until Month 27 (Month 24, 27, 30 and 33 UFC values were 218, 1193, 1120 and 617 nmol/24h respectively). Despite showing at least partial control in UFC (a decrease of at least 50% compared to baseline) at all post-baseline time points, the patient discontinued due to unsatisfactory therapeutic effect on Day 936; Month 33 was the last available UFC assessment. The patient received pasireotide 900 µg b.i.d. throughout the extension until Day 936 without any documented missing doses.
- One patient with baseline UFC of 280.8 nmol/24h had mostly reduced UFC post-baseline until an increase at Month 33 (Month 27, 33 and 36 UFC values were 146, 8342 and 1108 nmol/24h, respectively; during this time the patient received pasireotide 1200 µg b.i.d. without any documented missing doses). The patient was still ongoing at the time of data cut-off.

7.5.2 Long-term improvements in clinical signs and symptoms of Cushing's disease

The improvements in studied signs and symptoms of Cushing's disease observed during the core phase of study B2305 were clinically relevant and sustained with longer follow-up in the extension. Examples are shown below for systolic BP (Figure 7-16), diastolic BP (Figure 7-17), weight (Figure 7-18), and total cholesterol (Figure 7-19), plotted with mean UFC levels over time (note both dose groups are combined in these plots). For example, mean systolic BP decreased from 133.5 mmHg at baseline to 123.6 at Month 18, 120.5 mmHg at Month 24 and 122.7 mmHg at Month 33, with mean decrease from baseline of 7.9, 11.3 and 9.1 mmHg at the respective time points. Patients' mean weight decreased from 81.6 kg at baseline to 72.9 kg at Month 18, 73.6 kg at Month 24 and 72.1 kg at Month 33, with mean decrease from baseline of 7.6, 8.7 and 8.0 kg at the respective time points.

The improvement in clinical signs and symptoms of Cushing's disease that were associated with reductions of UFC further supports the clinical benefit offered by pasireotide. Clinical improvements in patients that do not normalize UFC but experience decreases in UFC represent an important finding not previously established.

Figure 7-16 **Mean (+/-SE) UFC (nmol/24h) and systolic blood pressure (mmHg) up to Month 33 (B2305)**

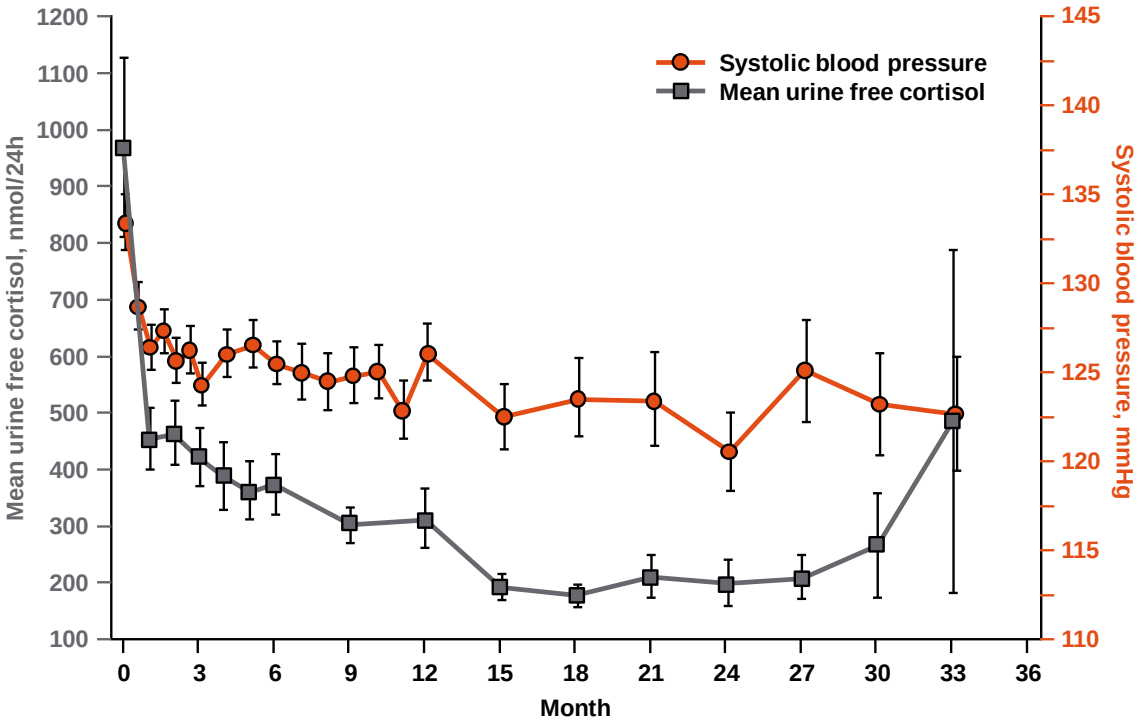


Figure 7-17 **Mean (+/-SE) UFC (nmol/24h) and diastolic blood pressure (mmHg) up to Month 33 (B2305)**

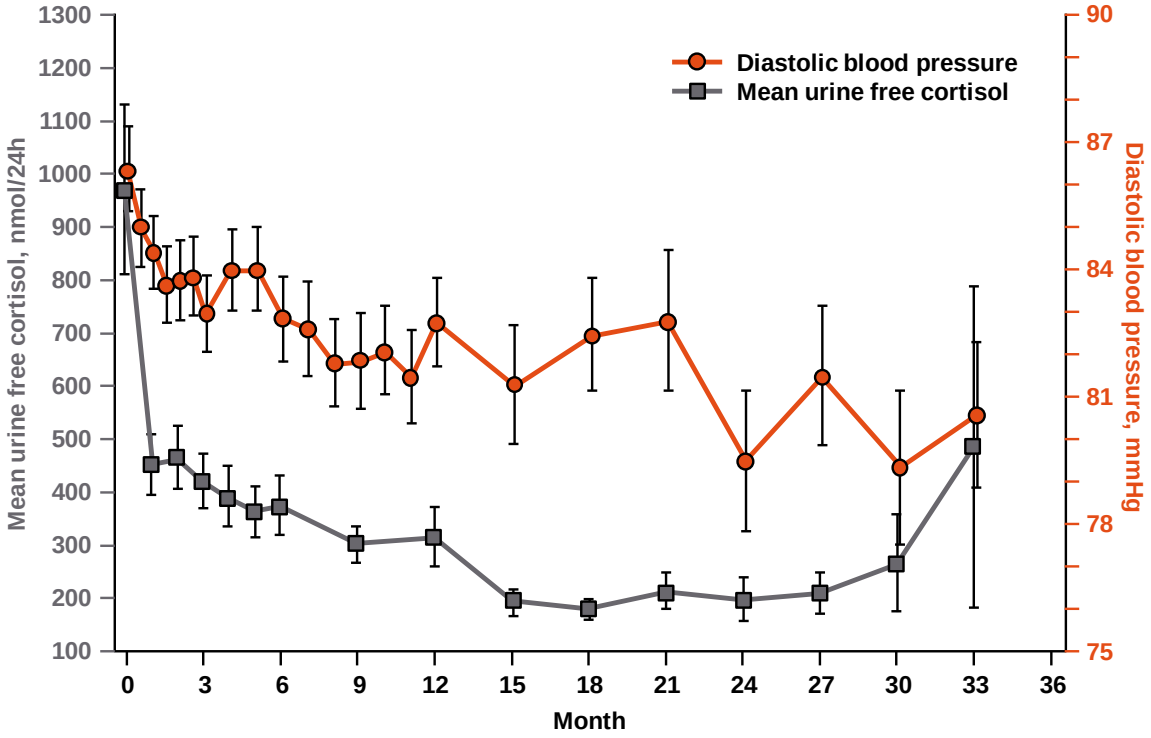


Figure 7-18 **Mean (+/-SE) UFC (nmol/24h) and weight (kg) up to Month 33 (B2305)**

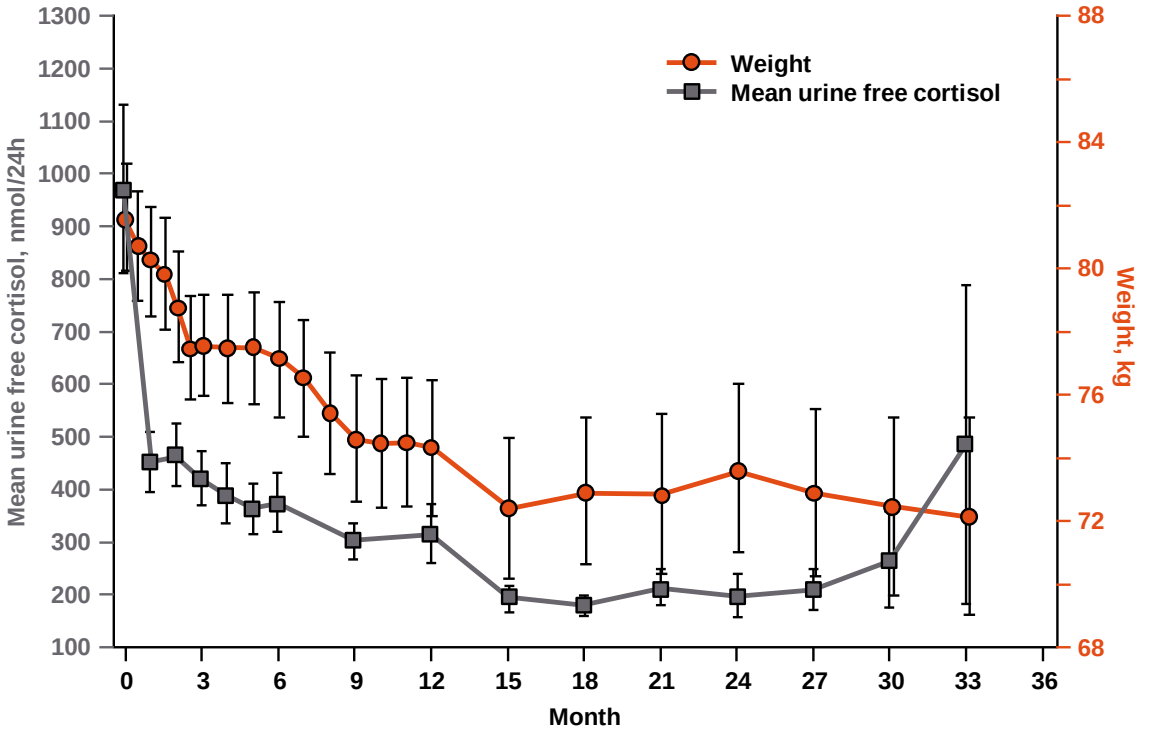
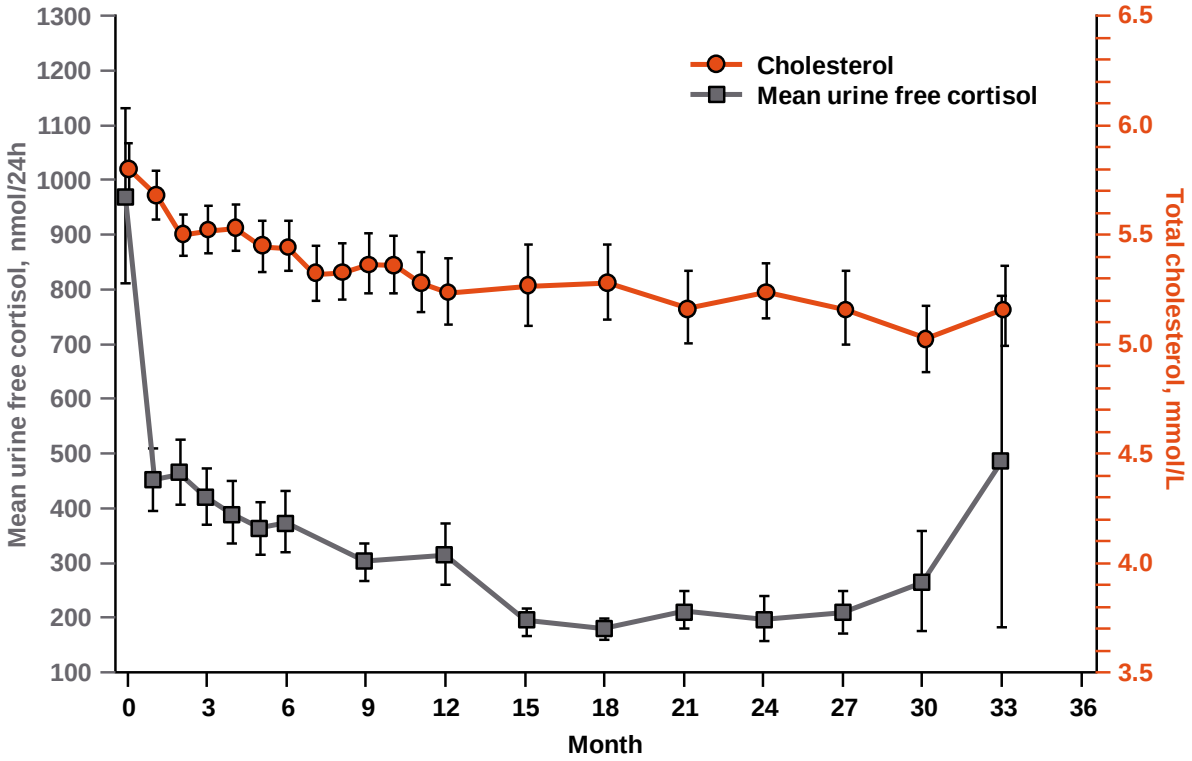


Figure 7-19 **Mean (+/-SE) UFC (nmol/24h) and total cholesterol (mmol/L) up to Month 33 (B2305)**



7.5.3 Effects post-discontinuation

Following discontinuation of therapy, an increase in UFC and other hormonal indicators of Cushing's disease are expected, as are worsening of signs and symptoms of the disease.

Patients who discontinued pasireotide in studies B2305, B2208, and its extension B2208E were followed for safety up to 28 days after discontinuation, however the studies were not designed to assess rebound effect after discontinuation of therapy. There did not appear to be any AEs suggesting withdrawal effects. Information on UFC is only available for a subset of patients in B2305 and only for 28 days post discontinuation. Available data do not support any definitive conclusions regarding a withdrawal effect.

7.6 Efficacy conclusions

Results from the Phase III study B2305 and the proof-of-concept Phase II study B2208 with its extension B2208E show that pasireotide treatment induced clinically relevant improvements in UFC levels and other measures of disease activity in patients with Cushing's disease. The reduction in mean UFC in both studies was rapid, robust, and sustained with long-term treatment, and the majority of patients had decreases in their UFC levels with treatment.

In Study B2305, the 900 µg b.i.d. dose group met the primary efficacy endpoint while the 600 µg b.i.d. dose group did not. The response rates (defined as normalization of UFC in patients without dose increase) in the primary efficacy analysis were 14.6% and 26.3% in the 600 and

900 µg b.i.d. dose groups. The proportion of patients who were either controlled or partially controlled at Month 6 was 34.1% and 41.3% in the 600 and 900 µg b.i.d. group, respectively; at Month 12 the results were 29.3% and 27.5%, respectively. The lower response rates in the 600 µg b.i.d. group relative to the 900 µg b.i.d. group can in part be attributed to the higher baseline mean UFC in this group.

It is important to consider that consistent and meaningful reductions in UFC were seen in both dose groups within the first month of treatment. Both dose groups achieved similar reductions in UFC (median % change from baseline to Month 6 was 47.9% in both dose groups). The reductions in UFC were sustained over time for patients who remained on treatment, and are considered clinically meaningful not only for patients achieving normal UFC levels. It should also be noted that as the decrease in UFC occurred rapidly, patients unlikely to achieve biochemical control can be identified relatively early.

Importantly, suppression of ACTH levels was observed in both dose groups in B2305 as well as in B2208, confirming the pituitary-targeted mechanism of pasireotide. In addition, decrease in tumor volume was observed in B2305 in patients with measurable tumor volume at baseline.

In B2305, the decreases in UFC and other biochemical indicators were accompanied by improvements in clinical signs and symptoms of hypercortisolism and in patients' quality of life. The improvements in systolic and diastolic BP, weight, BMI, lipids (total cholesterol, LDL and triglycerides with little change in HDL) and other parameters were clinically relevant, and it should be noted that BP decreased primarily in patients with hypertension at baseline but not in normotensive patients. Cushing's disease-related quality of life improved during treatment, as shown by an increase in CushingQOL scores. Importantly, improvements in clinical signs and symptoms as well as CushingQOL were sustained up to 12 months and were observed in patients experiencing reductions in UFC even if complete normalization did not occur.

Taken together, the results from study B2305 and B2208 show that pasireotide is an efficacious, pituitary-targeted therapy for the treatment of Cushing’s disease.

8 Overview of Safety of Pasireotide

The safety review for pasireotide s.c. in patients in Cushing's disease included a total of 201 patients and focuses on the results from the Phase III study B2305, with additional safety data available from the Phase II study B2208 with its extension B2208E. In addition, safety data for pasireotide s.c. in other indications and from studies in healthy volunteers is presented from 2 studies in patients with acromegaly (B2103 and B2201 with its extension B2201E), one study in carcinoid syndrome (B2202), as well as 7 studies in healthy volunteers and 5 special safety studies (Table 5-1, Table 6-1).

The total safety populations in these studies included all patients/healthy volunteers who received at least one dose of pasireotide and comprises a total of 726 subjects. This included 201 patients with Cushing’s disease (162 patients in study B2305, and 39 patients in study B2208, of which 19 patients continued in the optional extension) and 117 patients with other conditions (72 patients with acromegaly from studies B2103 and B2201 with extension B2201E and 45 patients with carcinoid syndrome from study B2202). In special safety studies

there were 158 healthy volunteers (127 pasireotide-treated) in the QT/QTc profile study B2113, 34 subjects (15 healthy volunteers and 19 patients with hepatic impairment) in the hepatic impairment study B2114, 90 healthy male volunteers in the glucose metabolism study B2124, 112 healthy male and female volunteers in the TQT study B2125, and 45 healthy male volunteers in an investigator-led glucose metabolism study B2216.

No pooling of data from these studies was performed due to differences in study design and patient populations.

Safety data derived from these studies support the acceptable safety and tolerability profile of pasireotide; in these studies, the doses and duration tested were considered appropriate to the relevant patient population. In addition, the safety of pasireotide in the Cushing's disease patient population is consistent with and supported by experience in acromegaly and carcinoid syndrome patients. The safety profile of pasireotide seen across the pasireotide development program is in line with the known class effects of somatostatin analogs. These effects include hyperglycemia, gastrointestinal disturbances, cholelithiasis, QT prolongation, bradycardia, cortisol withdrawal syndrome, abnormal liver function and hematological abnormalities.

Presentation of safety data

The safety evaluation of pasireotide in patients with Cushing's disease focuses on the safety data from the Phase III study B2305 up to 17-Mar-2010, by which time all patients had completed the core phase of the study (i.e at least 12 months of treatment) or discontinued early.

Additional long-term safety data is available from B2305 with a data cut-off of 30-Dec-2011, at which patients who were still followed in the study had completed at least 33 study months of treatment, and from the Phase II extension study B2208E.

An integrated analysis of safety data is presented for the following safety topics of special interest:

- Hyperglycemia
- LFT increases
- QT prolongation
- Hypocortisolism/Cortisol withdrawal syndrome

8.1 Safety assessment in B2305

The safety of pasireotide in study B2305 was evaluated for the following:

- Frequency, type (by system organ class (SOC) and preferred term), severity and causal relationship of AEs to study drug
- Deaths, frequency of SAEs and clinically notable AEs (which include AEs leading to discontinuation and AEs requiring dose reduction and/or interruption)
- Changes in clinical laboratory values observed after regular monitoring of hematology, clinical chemistry, and urinalysis (with particular attention to grade 3 or 4 laboratory abnormalities)
- Assessments of ECGs, vital signs, and physical condition

- Assessment of the gallbladder by ultrasound

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Increased risks associated with somatostatin analog treatment, such as hyperglycemia, gastrointestinal disturbances, cholelithiasis, QT prolongation, bradycardia, cortisol withdrawal syndrome, and abnormal liver function, were given particular emphasis when assessing and analyzing the data.

8.1.1 Safety population and exposure to pasireotide

The safety population in study B2305 comprised all 162 patients (82 patients randomized to 600 µg b.i.d. and 80 patients randomized to 900 µg b.i.d.).

The mean duration of exposure was approximately 10 and a half months in both treatment groups at the time of the 17-Mar-2010 data cut-off.

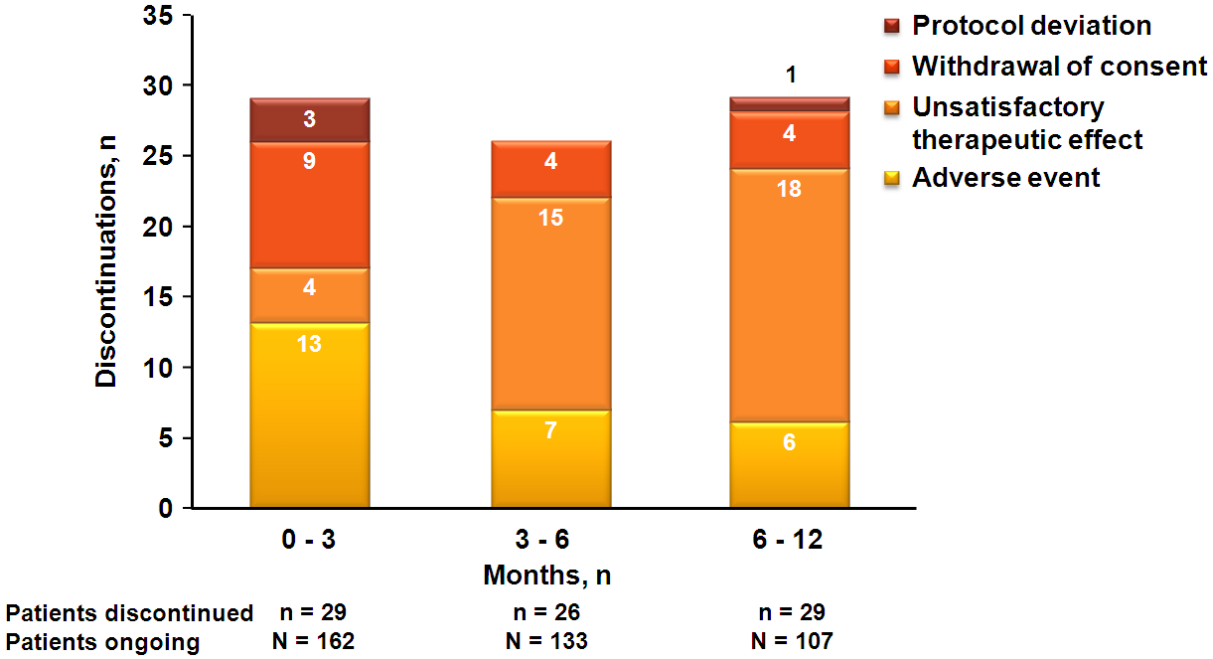
Table 8-1 Duration of exposure to pasireotide (B2305)

	Pasireotide 600 µg b.i.d. N=82 n (%)	**Pasireotide 900 µg b.i.d. N=80 n (%)**
Exposure category (months)		
≥ 1	76 (92.7)	74 (92.5)
≥ 2	72 (87.8)	69 (86.3)
≥ 3	68 (82.9)	64 (80.0)
≥ 4	65 (79.3)	60 (75.0)
≥ 5	59 (72.0)	57 (71.3)
≥ 6	55 (67.1)	55 (68.8)
≥ 9	45 (54.9)	45 (56.3)
≥ 12	28 (34.1)	35 (43.8)
≥ 15	20 (24.4)	16 (20.0)
≥ 18	15 (18.3)	11 (13.8)
≥ 21	7 (8.5)	9 (11.3)
≥ 24	6 (7.3)	7 (8.8)
Exposure (months)		
Mean	10.66	10.89
SD	7.645	8.232
Median	10.58	10.22
Min	0.03	0.03
Max	31.1	37.8

Duration of exposure = (date of last dose – date of first dose + 1) * 12 / 365.25.

Discontinuations due to AE and withdrawal of consent were more common in the first 3 months of treatment than later in the study for both dose groups combined (Figure 8-1). Discontinuations due to lack of efficacy mainly occurred after the first 3 months of therapy.

Figure 8-1 Reason for discontinuations (B2305)



8.1.2 Overview of adverse events

An overview of AEs in Study B2305 is shown in Table 8-2. About half of all patients had AEs that were grade 3 or 4, however relatively few patients had AEs leading to discontinuation (17.3% overall).

Table 8-2 Overview of adverse events (B2305)

	Pasireotide 600 µg b.i.d. N=82 n (%)	Pasireotide 900 µg b.i.d. N=80 n (%)
Adverse events (AEs)	80 (97.6)	79 (98.8)
Study drug-related AEs	79 (96.3)	76 (95.0)
Discontinued due to AEs	13 (15.9)	15 (18.8)
Grade 3 or 4 AEs	39 (47.6)	40 (50.0)

AEs up to data cut-off by SOC are shown in Table 8-3. Most patients (98.1%) experienced at least one AE. The SOCs with the highest frequencies were gastrointestinal disorders (80.9%), metabolism and nutrition disorders (74.7%), and general disorders and administration site conditions (54.3%). In general, the frequencies of AEs by SOC were comparable between the two groups.

Table 8-3 Adverse events, regardless of study drug relationship, by primary system organ class (B2305)

Primary system organ class	Pasireotide 600 µg b.i.d. N=82 n (%)	Pasireotide 900 µg b.i.d. N=80 n (%)
Patients with any AE(s)	80 (97.6)	79 (98.8)
Gastrointestinal disorders	64 (78.0)	67 (83.8)
Metabolism and nutrition disorders	61 (74.4)	60 (75.0)
General disorders and administration site conditions	46 (56.1)	42 (52.5)
Investigations	38 (46.3)	36 (45.0)
Infections and infestations	36 (43.9)	37 (46.3)
Nervous system disorders	32 (39.0)	34 (42.5)
Skin & subcutaneous tissue disorders	34 (41.5)	31 (38.8)
Hepatobiliary disorders	30 (36.6)	29 (36.3)
Musculoskeletal and connective tissue disorders	31 (37.8)	26 (32.5)
Vascular disorders	16 (19.5)	19 (23.8)
Psychiatric disorders	8 (9.8)	22 (27.5)
Endocrine disorders	15 (18.3)	15 (18.8)
Eye disorders	15 (18.3)	12 (15.0)
Injury, poisoning & procedural complications	10 (12.2)	17 (21.3)
Cardiac disorders	14 (17.1)	6 (7.5)
Renal and urinary disorders	12 (14.6)	6 (7.5)
Respiratory, thoracic and mediastinal disorders	10 (12.2)	7 (8.8)
Blood & lymphatic system disorders	5 (6.1)	10 (12.5)
Reproductive system and breast disorders	9 (11.0)	6 (7.5)
Ear and labyrinth disorders	4 (4.9)	8 (10.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (2.4)	3 (3.8)
Immune system disorders	2 (2.4)	1 (1.3)
Pregnancy, puerperium and perinatal conditions	1* (1.2)	0

*Patient underwent elective abortion on Day 186 (last dose of study medication on Day 148)

8.1.3 Most frequently occurring adverse events

By preferred term, the most frequent AEs in both dose groups were diarrhea (58.0%), nausea (51.9%), hyperglycemia (40.1%), and cholelithiasis (30.2%). The majority of these events were grade 1 or 2 (Table 8-4). The preferred term findings were generally balanced between the two dose groups with minor differences in frequencies of some preferred terms between the two groups.

Hyperglycemia and diabetes mellitus were slightly more frequent in the 900 µg b.i.d. group than the 600 µg b.i.d. group, and these were also the most frequent grade 3/4 AEs in both groups.

Table 8-4 Frequent adverse events (more than 10% of patients in any group) (B2305)

	Pasireotide 600 µg b.i.d. N=82 n (%)		Pasireotide 900 µg b.i.d. N=80 n (%)	
	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Diarrhea	48 (58.5)	3 (3.7)	46 (57.5)	2 (2.5)
Nausea	38 (46.3)	1 (1.2)	46 (57.5)	3 (3.8)
Hyperglycemia	31 (37.8)	8 (9.8)	34 (42.5)	13 (16.3)
Cholelithiasis	25 (30.5)	1 (1.2)	24 (30.0)	1 (1.3)
Headache	23 (28.0)	1 (1.2)	23 (28.8)	2 (2.5)
Abdominal pain	19 (23.2)	1 (1.2)	20 (25.0)	2 (2.5)
Fatigue	12 (14.6)	1 (1.2)	19 (23.8)	2 (2.5)
Diabetes mellitus	13 (15.9)	6 (7.3)	16 (20.0)	6 (7.5)
Nasopharyngitis	10 (12.2)	0	11 (13.8)	0
Alopecia	10 (12.2)	0	10 (12.5)	0
Asthenia	13 (15.9)	2 (2.4)	5 (6.3)	2 (2.5)
Glycosylated haemoglobin increased	10 (12.2)	1 (1.2)	8 (10.0)	0
ALT increased	11 (13.4)	1 (1.2)	6 (7.5)	3 (3.8)
GGT increased	10 (12.2)	4 (4.9)	7 (8.8)	2 (2.5)
Edema peripheral	9 (11.0)	0	8 (10.0)	0
Abdominal pain upper	10 (12.2)	0	6 (7.5)	0
Decreased appetite	7 (8.5)	0	9 (11.3)	0
Hypercholesterolemia	7 (8.5)	0	9 (11.3)	0
Hypoglycemia	12 (14.6)	3 (3.7)	3 (3.8)	0
Type 2 diabetes mellitus	10 (12.2)	4 (4.9)	5 (6.3)	3 (3.8)
Anxiety	5 (6.1)	0	9 (11.3)	0
Influenza	9 (11.0)	0	5 (6.3)	0
Insomnia	3 (3.7)	0	11 (13.8)	0
Myalgia	10 (12.2)	1 (1.2)	4 (5.0)	0

8.1.4 AEs requiring treatment discontinuation and dose adjustment or interruption

A total of 28 patients had at least one AE leading to discontinuation; 13 patients (15.9%) in the 600 µg b.i.d. group and 15 patients (18.8%) in the 900 µg b.i.d. group.

The most common AEs leading to discontinuation overall were (in the 600 and 900 µg b.i.d. groups) GGT increased (3.7% and 2.5% of patients), hyperglycemia (2.4% and 3.8% of patients), and diabetes mellitus (2.4% and 2.5% of patients).

A total of 55 patients had at least one AE requiring dose adjustment or study drug interruption; 31 patients (37.8%) in the 600 µg b.i.d. group and 24 patients (30.0%) in the 900 µg b.i.d. group.

Overall, the most common AEs leading to dose adjustment or interruption of study drug were (in the 600 and 900 µg b.i.d. groups) nausea (4.9% and 8.8% of patients), diarrhea (7.3% and 2.5% of patients), hyperglycemia (3.7% and 6.3% of patients), and adrenal insufficiency (4.9% and 5.0% of patients).

8.1.5 Deaths

In study B2305, no deaths occurred during 'active' treatment; however, one patient died in the screening phase and a second patient died approximately 2 months after discontinuation of study medication. The patient who died during screening never received study medication and the death was reported as being due to the progression of the concomitant disease (dementia). The second patient was randomized to the 900 µg b.i.d. group and received treatment for 6 and a half months before discontinuing due to unsatisfactory treatment effect. The patient underwent bilateral adrenalectomy 4 weeks after stopping study treatment, and died 5 weeks after surgery due to acute renal failure and disseminated intravascular coagulation as complications of the bilateral adrenalectomy. The investigator did not suspect a relationship to study drug. The patient had a month 6 assessment based on 2 UFC samples (less than the 3 needed to calculate mean UFC as per the analysis plan); the mean UFC was 348.5 nmol/24h.

8.1.6 Serious adverse events

Overall, SAEs were reported for 24.7% of patient; of these patients only about half had SAEs that were attributed to pasireotide treatment by the investigator (Table 8-5). Few patients discontinued the study as a results of an SAE.

Table 8-5 Serious adverse events (B2305)

	Pasireotide 600 µg b.i.d. N=82 n (%)	Pasireotide 900 µg b.i.d. N=80 n (%)
Deaths	0	0
Serious adverse events (SAEs)	19 (23.2)	21 (26.3)
Study drug related SAEs	7 (8.5)	12 (15.0)
Discontinued due to SAEs	3 (3.7)	5 (6.3)

The most common SAE reported in both dose groups was "Pituitary-dependent Cushing's syndrome" (3.7% of all patients; Table 8-6). This was the MedDRA term most frequently reported for cases where patients were hospitalized for surgical treatment for Cushing's disease within 30 days of discontinuing from the study.

There were 9 patients for whom an SAE of "Pituitary-dependent Cushing's syndrome", "Pituitary tumour benign" or "Secretory adenoma of pituitary" was reported. Eight of these patients were discontinued from the study and then had surgical interventions (pituitary surgery or bilateral adrenalectomy) for the treatment of Cushing's disease, for which they were hospitalized within 30 days of treatment discontinuation; these events were considered as SAEs due to the hospitalization. For 1 patient, the SAE "Pituitary tumour benign" was the underlying reason for an SAE of nerve paralysis and was thus reported as an SAE as well.

None of these SAEs was considered related to the study drug by the investigator.

Table 8-6 Serious adverse events (at least 2 patients in any treatment group) (B2305)

	Pasireotide 600 µg b.i.d. N=82 n (%)	Pasireotide 900 µg b.i.d. N=80 n (%)
Patients with any SAE(s)	**19 (23.2)**	**21 (26.3)**
Pituitary-dependent Cushing's syndrome	3 (3.7)	3 (3.8)
Diabetes mellitus	1 (1.2)	3 (3.8)
Hyperglycaemia	1 (1.2)	3 (3.8)
Cholelithiasis	3 (3.7)	1 (1.3)
Pituitary tumour benign	1 (1.2)	2 (2.5)
Adrenal insufficiency	0	2 (2.5)

SAEs that were related to study drug occurred in 19 patients (11.7%); 7 patients (8.5%) in the 600 µg b.i.d. group and 12 patients (15.0%) in the 900 µg b.i.d. group.

The most frequent study drug-related SAEs were those related to glucose metabolism (9 patients) and the gall bladder (6 patients).

Among the 9 patients with SAEs related to glucose-metabolism, diabetes mellitus and hyperglycemia were each reported for 1 patient in the 600 µg b.i.d. group and 3 patients in the 900 µg b.i.d. group, and type 2 diabetes mellitus was reported for 1 patient in the 600 µg b.i.d. group. Of these 9 patients, 5 had active diabetes at study entry.

Of the 6 patients with SAEs related to the gall bladder, 4 patients had cholelithiasis (3 patients in the 600 µg b.i.d. group and 1 patient in the 900 µg b.i.d. group); in addition, 1 patient in each group had cholecystitis/cholecystitis acute. Three of these 6 patients underwent cholecystectomy during the study; none of them discontinued due to the event.

Eight patients had SAEs leading to discontinuation; 3 patients (3.7%) in the 600 µg b.i.d. group and 5 patients (6.3%) in the 900 µg b.i.d. group. SAEs leading to discontinuation in the 600 µg b.i.d. group were lipase increased, diabetes mellitus, and pregnancy. In the 900 µg b.i.d. group SAEs leading to discontinuation were adrenal insufficiency, pituitary-dependent Cushing’s syndrome, ECG QT prolonged, hyperglycemia, pituitary tumor benign, cranial nerve paralysis, and tongue paralysis (the last 3 SAEs were all in the same patient).

8.1.7 Laboratory parameters

Clinical laboratory parameters (standard hematology, biochemistry and urinalysis, including FPG) were measured at baseline and monthly in study B2305; HbA1c was measured at baseline and then every 2 months. In addition, coagulation parameters and thyroid function parameters were assessed at baseline and every 3 months, plus one assessment after one month of treatment.

Changes in clinical laboratory values from baseline over time were evaluated, including shifts to extreme values during the study.

Hematology

Most abnormalities in hematology parameters were grade 1. The most frequently reported abnormalities were partial thromboplastin time and international normalized ratio (INR), of which a grade 1 abnormality was reported for 33.3% and 20.0% of all patients.

Biochemistry

A detailed discussion for parameters indicative of hyperglycemia (FPG, HbA1c) and LFTs (ALT, AST, total bilirubin) is provided in dedicated sections below.

No consistent or clinically relevant changes in other biochemistry parameters were observed in B2305, with the majority of abnormalities being grade 1.

8.1.8 Gallbladder ultrasound and cholelithiasis

Examination of gallbladder by means of ultrasonography was performed at baseline and every 6 months thereafter in study B2305.

The proportion of patients with normal gallbladder ultrasound results was 84.6% at baseline, and decreased to 51.2% at the last post-baseline assessment. Of the 137 patients with normal gallbladder ultrasound at baseline, 9 had detectable sludge and 27 had gallstones at their last assessment (18 patients had no last gallbladder ultrasound result). The 12 patients with gallstones at baseline still had gallstones at their last assessment. No patient had intra- or extra-hepatic ductal dilatation.

The results for gallbladder ultrasound were comparable between the 600 µg b.i.d. and 900 µg b.i.d. dose groups.

Cholelithiasis was reported by 49 patients (30.2%); with the exception of 2 patients all had grade 1-2 events. The event was serious for 4 patients (2 of them underwent cholecystectomy during the study, for the other 2 the event was ongoing at data cut-off). One patient discontinued due to cholelithiasis.

8.1.9 Vital signs and physical examinations

Vital sign abnormalities were uncommon in B2305, each affecting fewer than 10% of patients overall at the time of data cut-off. The most common abnormalities were increased diastolic BP (8.8% overall) and a low seated pulse rate (8.2% overall). All other abnormalities were reported by fewer than 4% of all patients.

8.2 Safety in supportive Phase II study B2208

In study B2208, treatment with pasireotide 600 µg b.i.d. for 15 days was generally well tolerated, with safety findings that were consistent with other somatostatin analogs and previous clinical studies with pasireotide. The majority of patients experienced one or more AEs, with the highest incidence observed for gastrointestinal AEs, such as diarrhea (51.3%) and nausea (30.8%). Most of the events were grade 1 or 2. No deaths occurred, and SAEs were reported for 3 patients.

As expected in patients with Cushing's disease, hyperglycemia was observed both at baseline, and more frequently after treatment with pasireotide. A trend towards attenuation of the

hyperglycemic effects over time was evidenced by smaller post-prandial increases in glycemia (on Days 5, 12 and 15 relative to Day 1) and fewer patients having shifted to a higher glucose level at the end of the study (relative to the highest level any time).

Serum ALT and GGT levels were mildly increased in some patients. No patient had a >3×ULN increase in liver chemistry tests and there were no cases that met diagnostic criteria for Hy's law.

There were no other clinically meaningful changes in hematology or biochemistry and no obvious trends in changes in vital signs or ECG parameters.

8.3 Blood glucose and HbA1c

8.3.1 Mechanism of hyperglycemia

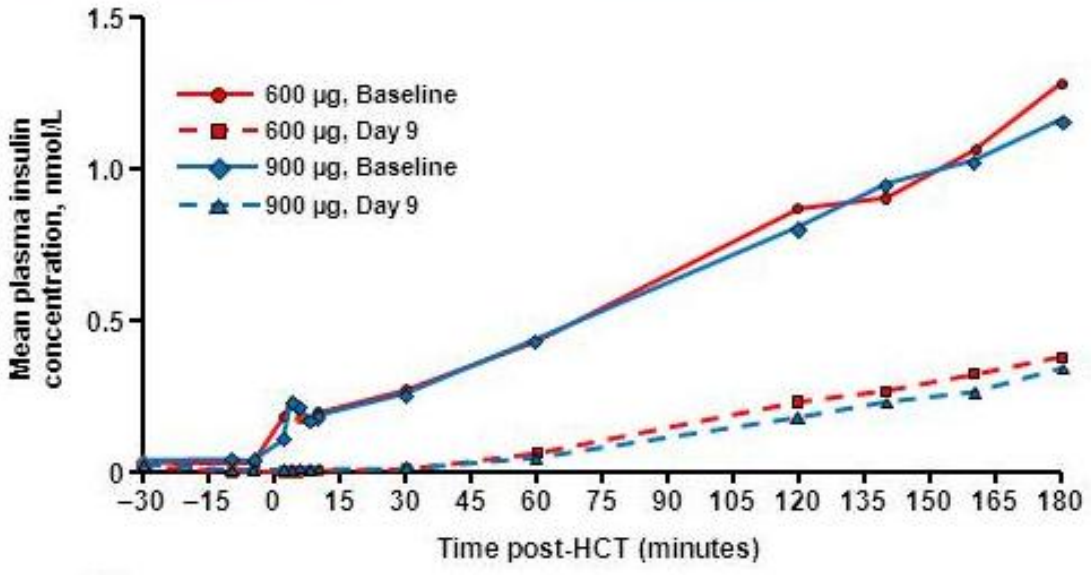
Cushing's disease is characterized by hypercortisolism resulting from an ACTH-secreting pituitary tumor. Excess cortisol is known to affect metabolism through a variety of mechanisms, such as redistribution of free fatty acids to central fat, increased gluconeogenesis, inhibition of glucose uptake by peripheral tissues and impairment of insulin function. Insulin resistance is invariably present in patients with Cushing disease, and impaired glucose tolerance is seen in 60% of patients (Chanson and Salenave 2010).

Hyperglycemia is a well documented class effect of somatostatin analogs, and dysglycemia (hyperglycemia/hypoglycemia) events have been reported as adverse reactions for octreotide (Sandostatin®) and lanreotide (Somatuline®). For pasireotide, a hyperglycemic effect was evident from preclinical studies, where in rats, single-dose pasireotide acutely elevated plasma glucose. The effect was transient (<8 hours) with rapid tachyphylaxis after repeated administration. Continuous s.c. infusion of pasireotide caused small and transient elevations of glucose.

In Phase I studies in healthy volunteers, the administration of pasireotide s.c. caused an asymptomatic, rapid (within 30 minutes) and transient (lasting approximately 6 − 8 hours) hyperglycemia in both fasting and post-prandial conditions. The effect on postprandial blood glucose levels was more pronounced at pasireotide doses greater than 600 µg b.i.d.; however it was transient as well.

The effect of pasireotide treatment on glycemia, the underlying mechanism, and optimal measures for management have been investigated in several Phase I and II studies. Recent results from the comprehensive mechanistic study B2216 in healthy volunteers confirmed that the hyperglycemia is primarily a consequence of decreased secretion of insulin and incretins (glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)), with no changes in hepatic or peripheral insulin sensitivity. This is illustrated for insulin in Figure 8-2, which shows that the increase in mean plasma insulin levels during hyperglycemic clamp on Day 9 was delayed compared to baseline, and that the rate of increase was slower and the final insulin concentration was less than a third of the concentration achieved pre-pasireotide treatment. The corresponding results for glucagon are shown in Figure 13-4 in Appendix II. Finally, results of hyperglycemic-euglycemic clamp test results demonstrated that pasireotide had no effect on glucose disposal rate, demonstrating that pasireotide does not impact insulin sensitivity (see Figure 13-5 in Appendix II).

Figure 8-2 Mean plasma insulin levels during hyperglycemic clamp (B2216)



The hyperglycemic effect is in line with pasireotide's receptor binding profile. In humans, inhibition of insulin secretion from pancreatic islet cells is mediated mainly by SSTR2 and SSTR5, whereas the inhibition of glucagon secretion is mediated almost entirely by SSTR2. Higher affinity of pasireotide to SSTR5 than SSTR2 leads to relatively stronger inhibition of insulin than glucagon, which explains the stronger hyperglycemic effect observed with pasireotide compared to other somatostatin analogs that bind avidly to SSTR2, but have lower binding affinity for SSTR5.

Results from study B2107 in healthy volunteers showed that in the fasting state, pasireotide induced a marked decrease in insulin, a smaller decrease in glucagon and an increase in FPG. When pasireotide was given after a breakfast meal, the decrease in insulin was smaller than in the fasting state. Results from study B2208 in patients with Cushing's disease were comparable to those from B2107, however both fasting and post-prandial glucose levels were consistently higher in Cushing's disease patients than in the healthy volunteers.

Results from the recently conducted study B2124 corroborate that the underlying mechanisms of hyperglycemia following pasireotide s.c. treatment in humans are mainly due to decreased insulin secretion and reduced GLP-1 and GIP incretin secretion with no changes in hepatic or peripheral insulin sensitivity. In this study healthy volunteers were co-administered pasireotide 600 µg b.i.d. either alone or with one of 4 different classes of antihyperglycemic drugs (biguanide [metformin], insulin secretagogue [nateglinide], DPP-4 inhibitor [vildagliptin], and GLP-1 analog [liraglutide]) for 7 days. On Day 7, plasma glucose AUC post-OGTT increased by 69% compared to baseline with pasireotide alone. This effect was reduced by 13%, 29%, 45% and 72% with co-administration of metformin, nateglinide, vildagliptin and liraglutide, respectively. Similarly, compared with pasireotide alone, insulin levels were increased by a mean of 71% and 34% when pasireotide was co-administered with vildagliptin and liraglutide, respectively; only minimal increases were seen after co-administration with metformin (6%) and nateglinide (3%). However, as hypoglycemia was observed during nateglinide treatment, this treatment may also be effective in some cases.

These results suggest that incretin based therapies (i.e. GLP-1 analogs and DPP-4 inhibitors) would be most useful in the management of pasireotide-induced hyperglycemia. In view of the pre-existing insulin resistance in patients with Cushing's disease, combination therapy with a biguanide (eg metformin) and an incretin enhancer may also be appropriate to treat pasireotide-induced hyperglycemia.

Novartis is planning to evaluate the effect of proactive, intensive hyperglycemia management with focus on incretin-based therapy and metformin in a 24-week study (Study B2219) in patients with Cushing's disease receiving pasireotide treatment.

8.3.2 Hyperglycemia in Phase III study B2305

8.3.2.1 Patients' diabetic status at baseline

To better understand the glycemic effect of pasireotide in patients with Cushing's disease, patients were categorized according to their degree of glucose dysregulation at baseline, based on FPG and HbA1c levels (Diagnosis and Classification of Diabetes Mellitus, American Diabetes Association, 2010), prior history of diabetes, and use of anti-diabetic medication as follows:

- **Diabetic:** history of antidiabetic medication, prior history of diabetes mellitus, HbA1c ≥ 6.5%, or FPG ≥126 mg/dL
- **Pre-diabetic:** not diabetic, and 100 mg/dL ≤ FPG <126 mg/dL, or 5.7% ≤ HbA1c <6.5%
- **Normal glucose tolerance:** neither diabetic nor pre-diabetic, and FPG <100 mg/dL and/or HbA1c <5.7%

In agreement with the known predisposition for hyperglycemia among patients with Cushing's disease, more than half of all patients were either pre-diabetic (24.1%) or diabetic (34.0%) at baseline (Table 8-7). Note that among the 55 patients who were diabetic at baseline according to the above criteria, 22 patients (40.0%) were not receiving anti-diabetic therapy. The distribution of patients by diabetic status was balanced between the 600 µg b.i.d. and 900 µg b.i.d. dose groups (Table 8-8).

At last assessment, many patients had worsening of their diabetic status: of the 67 patients with normal glucose tolerance at baseline, 29 were pre-diabetic and 23 were diabetic. Among the 39 patients who were pre-diabetic at baseline, 9 were still pre-diabetic at their last assessment, and 28 were diabetic.

Improvements in diabetic status were also noted for a few patients: one patient who was pre-diabetic at baseline had normal glucose tolerance at last assessment. Among the 55 patients who were diabetic at baseline, 6 were classified as pre-diabetic at last assessment, and one patient had normal glucose tolerance.

Table 8-7 Changes from baseline in diabetic status (B2305)

Baseline category	Total N=162 n (%)	Patients in each category at last assessment* Normal n (%)	Pre-diabetic n (%)	Diabetic n (%)	Missing n (%)
Normal	67 (41.4)	14 (20.1)	29 (43.3)	23 (34.3)	1 (1.5)
Pre-diabetic	39 (24.1)	1 (2.6)	9 (23.1)	28 (71.8)	1 (2.6)
Diabetic	55 (34.0)	1 (1.8)	6 (10.9)	47 (85.5)	1 (1.8)
Missing	1 (0.6)	1 (100)	0	0	0

*Percentage is based on total in Baseline category

Diabetic: history of antidiabetic medication, prior history of diabetes mellitus (applicable to baseline definition only), HbA1c ≥ 6.5%, or FPG ≥126 mg/dL
Pre-diabetic: not diabetic, and 100 mg/dL ≤ FPG<126 mg/dL, or 5.7% ≤ HbA1c < 6.5%
Normal glucose tolerance: neither diabetic nor pre-diabetic, and FPG <100 mg/dL and/or HbA1c <5.7%

8.3.2.2 Hyperglycemia-related AEs

AEs related to changes in glycemia were evaluated using a special search category for hyperglycemia-related events. This category included 35 preferred terms associated with hyperglycemia from the SOCs "endocrine disorders", "metabolism and nutrition disorders", and "investigations". Examples of preferred terms that were identified included are “hyperglycemia”, ‘diabetes mellitus” and “blood glucose increased”.

The incidence of hyperglycemia-related AEs was highest in patients who were diabetic at baseline, followed by those who were pre-diabetic at baseline, and lowest in patients with normal glucose tolerance at baseline (Table 8-8). Similarly, grade 3-4 hyperglycemia-related AEs and SAEs were most frequent among diabetic patients, and in particular those in the 900 µg b.i.d. group. Grade 3-4 hyperglycemia-related events were infrequent in patients with normal glucose tolerance at baseline, regardless of dose group.

There were no cases of hyperglycemic emergency such as diabetic ketoacidosis or hyperglycemic hyperosmolar state (hyperosmolar coma) reported in study B2305.

Table 8-8 Hyperglycemia-related adverse events by diabetic status at baseline (B2305)

Hyperglycemia events	Normal glucose tolerance 600 µg b.i.d. N=35 n (%)	Normal glucose tolerance 900 µg b.i.d. N=32 n (%)	Pre-diabetes 600 µg b.i.d. N=18 n (%)	Pre-diabetes 900 µg b.i.d. N=21 n (%)	Diabetes 600 µg b.i.d. N=28 n (%)	Diabetes 900 µg b.i.d. N=27 n (%)
Any AE	21 (60.0)	16 (50.0)	13 (72.2)	15 (71.4)	26 (92.9)	26 (96.3)
Grade 3 or 4 AE	3 (8.6)	1 (3.1)	5 (27.8)	5 (23.8)	11 (39.3)	15 (55.8)
AEs leading to discontinuation	1 (2.9)	1 (3.2)	0	3 (14.3)	3 (10.7)	2 (7.4)
SAEs	1 (2.9)	0	1 (5.6)	1 (4.8)	2 (7.1)	5 (18.5)

Diabetic: history of antidiabetic medication, prior history of diabetes mellitus (applicable to baseline definition only), HbA1c ≥ 6.5%, or FPG ≥126 mg/dL
Pre-diabetic: not diabetic, and 100 mg/dL ≤ FPG<126 mg/dL, or 5.7% ≤ HbA1c < 6.5%
Normal glucose tolerance: neither diabetic nor pre-diabetic, and FPG <100 mg/dL and/or HbA1c <5.7%

AEs linked to hyperglycemia were reported for 74.4% and 71.3% of patients in the 600 and 900 µg b.i.d. groups (Table 8-9). The most frequent preferred terms overall were "hyperglycemia", "diabetes mellitus", and "glycosylated hemoglobin increased". Apart from hypoglycemia, which was predominantly reported in the 600 µg b.i.d. group, hyperglycemia-related events were generally comparable between the groups.

Ten patients discontinued due to hyperglycemia-related events (4 patients in the 600 µg b.i.d. and 6 patients in the 900 µg b.i.d. group. Evaluation of discontinuations by responder status at Month 6 showed that 9 of the 10 patients who discontinued were uncontrolled in terms of UFC, the tenth patient was partially controlled.

Among the 118 patients with hyperglycemia-related events, more than half (78 patients) had AEs that were maximally grade 1 or 2 in severity. Of the 40 patients with grade 3 or 4 events, most were grade 3 (38 patients) whereas only 2 patients had grade 4 events.

Hyperglycemia led to study drug dose adjustment or interruption in 3.7% and 6.3% of patients in the 600 and 900 µg b.i.d. groups, respectively.

Both diabetes mellitus and hyperglycemia were reported as SAEs for 3 patients in the 900 µg b.i.d. group and for 1 patient in the 600 µg b.i.d. group.

Table 8-9 Hyperglycemia-related adverse events (B2305)

	Pasireotide 600 µg b.i.d. N = 82		Pasireotide 900 µg b.i.d. N = 80	
	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Total	**61 (74.4)**	**19 (23.2)**	**57 (71.3)**	**21 (26.3)**
Hyperglycemia	31 (37.8)	8 (9.8)	34 (42.5)	13 (16.3)
Diabetes mellitus	13 (15.9)	6 (7.3)	16 (20.0)	6 (7.6)
Glycosylated hemoglobin increased	10 (12.2)	1 (1.2)	8 (10.0)	0
Hypoglycemia	12 (14.6)	3 (3.7)	3 (3.8)	0
Type 2 diabetes mellitus	10 (12.2)	4 (4.9)	5 (6.3)	3 (3.8)
Blood glucose increased	6 (7.3)	0	3 (3.8)	0
Blood insulin decreased	1 (1.2)	0	4 (5.0)	0
Glucose tolerance impaired	2 (2.4)	0	2 (2.5)	0
Glycosuria	0	0	1 (1.3)	0

Note: N = number of patients in safety analysis set.

A subject with multiple occurrences of an AE under one treatment arm is counted only once in the AE category for that treatment

8.3.2.3 Fasting plasma glucose

Mean FPG levels peaked at Month 1 in both dose groups, followed by a slight decrease and stabilization by Month 3 (Table 8-10).

Table 8-10 Mean fasting plasma glucose over time (B2305)

	Pasireotide 600 µg b.i.d.		Pasireotide 900 µg b.i.d.	
Visit	**n**	**Mean (SD) mg/dL**	**N**	**Mean (SD) mg/dL**
Baseline	79	98.6 (23.6)	79	97.0 (18.7)
Month 0.5	78	136.0 (57.0)	76	149.2 (68.1)
Month 1	76	138.8 (68.6)	72	153.4 (71.5)
Month 1.5	74	131.4 (57.0)	69	143.6 (57.0)
Month 2	70	133.7 (51.4)	67	138.4 (60.3)
Month 3	69	122.0 (41.5)	66	124.7 (52.1)
Month 4	68	122.1 (41.8)	61	124.9 (43.1)
Month 5	62	121.3 (33.9)	57	128.5 (46.3)
Month 6	57	125.1 (34.6)	55	128.0 (54.6)
Month 9	46	126.9 (35.9)	48	119.4 (33.1)
Month 12	39	120.9 (40.5)	38	114.4 (36.3)

8.3.2.4 Glycosylated hemoglobin

Mean HbA1c levels increased from baseline and stabilized after Month 2 (Table 8-11).

Table 8-11 Mean HbA1c over time (B2305)

	Pasireotide 600 µg b.i.d.		Pasireotide 900 µg b.i.d.	
Visit	**n**	**Mean (SD) %**	**N**	**Mean (SD) %**
Baseline	78	5.83 (0.78)	76	5.76 (0.79)
Month 2	73	7.24 (1.65)	66	7.41 (1.50)
Month 4	68	7.23 (1.49)	61	7.15 (1.17)
Month 6	59	7.24 (1.42)	56	7.34 (1.18)
Month 8	49	7.31 (1.46)	46	7.36 (1.38)
Month 10	43	7.37 (1.35)	47	7.15 (1.33)
Month 12	40	7.25 (1.32)	38	7.21 (1.60)

8.3.2.5 Measures of glycemia after treatment discontinuation

Analysis of FPG and HbA1c levels in patients who discontinued pasireotide treatment prior to Month 12 shows that the pasireotide-induced hyperglycemia was reversible (Table 8-12). The safety follow-up visit was performed 1 month after the last dose of pasireotide. Within this time frame, mean FPG levels returned to near-baseline levels in patients who discontinued treatment. HbA1c levels also decreased markedly despite the relatively short time that patients were off treatment. No further long-term data after discontinuation of treatment are available.

Table 8-12 Mean FPG and HbA1c after discontinuation of treatment (B2305)

	Pasireotide 600 µg b.i.d.		Pasireotide 900 µg b.i.d.	
Visit	**n**	**Mean (SD) %**	**n**	**Mean (SD) %**
Fasting plasma glucose				
Baseline	27	97.8 (20.51)	30	98.2 (20.76)
Last value prior to discontinuation	27	126.1 (36.92)	30	133.7 (55.05)
Safety follow-up	27	102.2 (23.00)	30	104.5 (22.02)
HbA1c				
Baseline	25	5.97 (0.829)	29	5.81 (0.902)
Last value prior to discontinuation	25	7.68 (1.203)	29	7.57 (1.594)
Safety follow-up	25	6.9 (1.002)	29	6.82 (1.606)

The Safety follow-up visit occurred 1 month after the patient received the last dose of pasireotide.

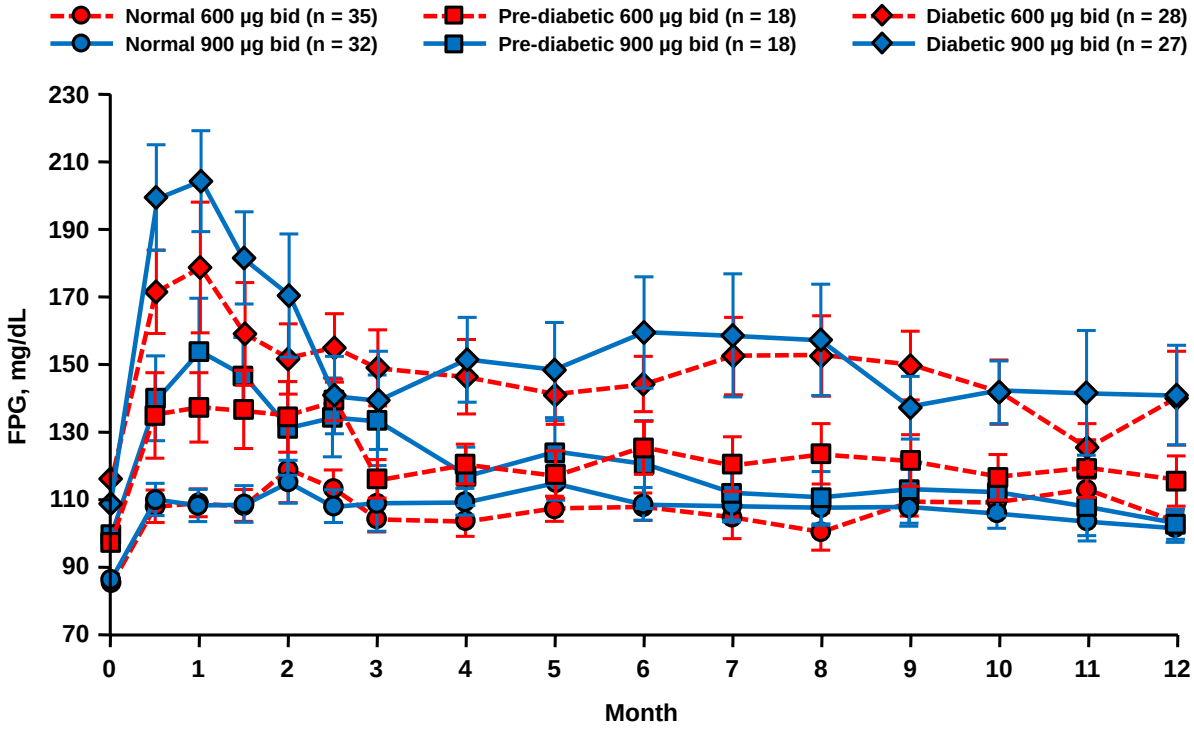
8.3.2.6 Measures of glycemia by diabetic status at baseline

Plots of FPG over time by patients' baseline diabetic status show that mean FPG increased to higher levels in the diabetic and pre-diabetic patients relative to those with normal glucose tolerance in both pasireotide dose groups (Figure 8-3).

In the diabetic patients FPG levels peaked within the first month of treatment. The peak was higher in patients randomized to the 900 µg b.i.d group than the 600 µg b.i.d group, but by Month 3 FPG levels had decreased to a similar level and remained comparable in both randomized dose groups up to Month 12. The peak change from baseline was smaller for pre-diabetic patients than diabetic patients, and mean FPG stabilized at a lower level. The smallest increase in FPG was seen for patients with normal glucose tolerance at baseline.

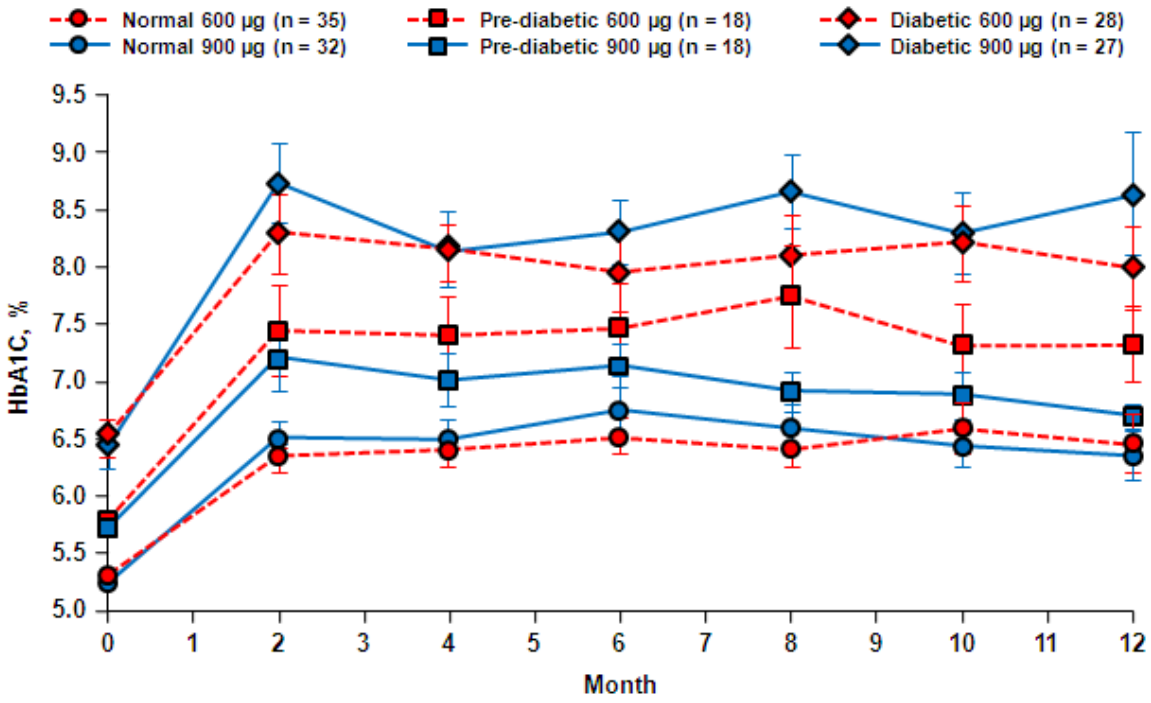
The plateau and decrease in FPG after Month 2 could be attributed to a combination of three factors: dose adjustments, antidiabetic interventions, and correction of hypercortisolism by the administration of pasireotide. However, the study was not designed to address the contributions of each of these factors.

Figure 8-3 Mean (+/-SE) FPG over time by baseline diabetic status and randomized pasireotide dose group (B2305)



Plots of HbA1c over time by patients' baseline diabetic status showed a comparable result to those of FPG. Mean HbA1c levels were higher at baseline in the diabetic and pre-diabetic patients relative to those with normal glucose tolerance, and increased to higher levels within the first 2 months of treatment. No further increase in HbA1c was seen thereafter for any of the groups (Figure 8-4).

Figure 8-4 Mean (+/-SE) HbA1c over time by baseline diabetic status and randomized pasireotide dose group (B2305)



8.3.2.7 Measures of glycemia by Month 6 responder status

FPG and HbA1c levels are shown by Month 6 responder status in Figure 8-5 and Figure 8-6, respectively. The hyperglycemic effect in terms of FPG was overall lower in responders than non-responders in both dose groups. For HbA1c, the hyperglycemic effect was smaller among responders than non-responders in the 600 µg b.i.d. group, whereas in the 900 µg b.i.d. group there was no difference between responder and non-responders.

Figure 8-5 **Mean (+/-SE) FPG over time by responder status and randomized pasireotide dose group (B2305)**

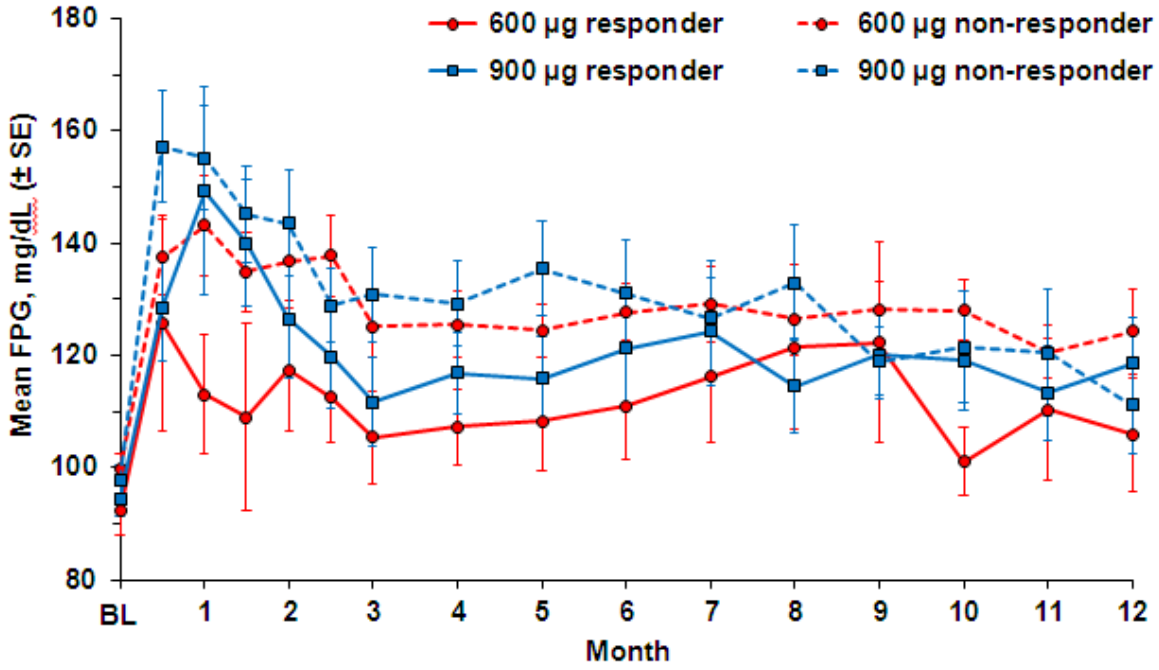
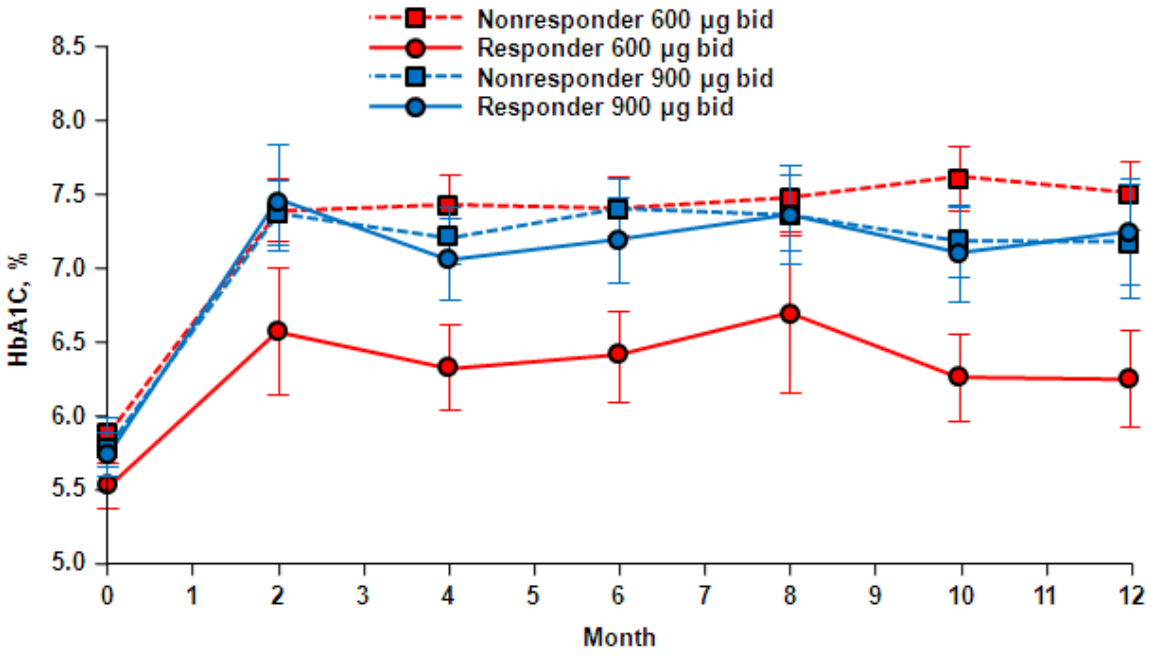


Figure 8-6 **Mean (+/-SE) HbA1c over time by responder status and randomized pasireotide dose group (B2305)**



Responder: Patients with UFC ≤ ULN at Month 6.
Non-responder: Patients with UFC > ULN at Month 6

8.3.2.8 Use of anti-diabetic medication

In an effort to better understand the role of anti-diabetic medications in the management of post-baseline hyperglycemia, the use of anti-diabetic medication, diabetic status at baseline and during the study, as well as FPG and HbA1c levels over time was analyzed in Study B2305.

Prior to randomization, 33 patients (20.4%) were taking anti-diabetic treatment. Among the 55 patients who were diabetic at baseline, 22 patients (40.0%) were not receiving anti-diabetic therapy. Of the 71 patients who met HbA1c $\geq$ 7% or consecutive FPG $\geq$ 130 mg/dL values at any time during study (not meeting biochemical criteria at baseline or on anti-diabetic medications at baseline), 28 did not receive anti-diabetic treatment. Of the 88 patients who achieved HbA1c $\geq$ 6.5% or consecutive FPG $\geq$ 126 mg/dL values at any time during study (not meeting biochemical criteria at baseline or on anti-diabetic medications at baseline), 43 patients did not receive anti-diabetic treatment.

FPG and HbA1c levels were analyzed by category of anti-diabetic medication used in study B2305. It is important to note, however, that there are several limitations related to these analyses, including the following:

- Post-baseline medications varied, as different sequences of mono- and combination therapies were used.
- Several medications were often used in conjunction, therefore the effect of individual medications is difficult to assess
- Dosing information was not collected

The following categories of anti-diabetic medications were defined:

1. **None:** Patients who never used anti-diabetic therapy post-baseline
2. **Oral agents only:** Patients who used only oral anti-diabetic therapy during the post-baseline period
   The "Oral agents only" category was further classified into two mutually exclusive categories:
   - **2a. Monotherapy Only:** Patients who used only single oral agent/s post-baseline. The 'Monotherapy only' category was also classified into mutually exclusive categories defined by the type of monotherapy (metformin only, sulfonylurea only, DPP-IV inhibitors only, glinides only, others) exclusively used throughout the post-baseline period
   - **2b. Multiple:** Patients who used multiple drugs simultaneously at any time post-baseline Patients who used multiple oral agents simultaneously at any time post-baseline (but never used insulin) were also grouped by the number of oral agents used (2, 3 or 4 oral agents). These groups are not necessarily mutually exclusive.
3. **Insulin at any time:** Patients who used insulin at any time during the post-baseline period, regardless of any other medication that may have been received.

Anti-diabetic medication use post baseline is summarized in Table 8-13 (note that this includes patients who were already receiving anti-diabetic medication at baseline). Half of all patients did not use any anti-diabetic medication during the study, 26.5% used oral anti-diabetic medications only, and 26.5% used insulin therapy at any time during the study.

Twenty patients (12.3%) were exclusively on monotherapy, and 14 of these patients received metformin monotherapy. 14.2% of patients were on combination therapy at some time during the post-baseline period.

Table 8-13 Use of anti-diabetic medications during the study (B2305)

Anti-diabetic medications used post-baseline	Overall N=162 n (%)
None	**76 (46.9%)**
Any anti-diabetic medication	**86 (53.1)**
Oral agent only	**43 (26.5)**
Monotherapy only	20 (12.3)
Monotherapy metformin only	14 (8.6)
Monotherapy sulfonylurea only	3 (1.9)
Monotherapy DPP-IV inhibitor only	0
Monotherapy glinides only (nateglinide, repaglinide)	1 (0.6)
Monotherapy other	2 (1.2)
Multiple	23 (14.2)
2 oral agents at any time	21 (13.0)
3 oral agents at any time	11 (6.8)
4 oral agents at any time	1 (0.6)
Insulin therapy at any time	**43 (26.5)**

No patient was treated with a DPP-IV or GLP-1 analog as monotherapy

Dosage of anti-diabetic medications was not collected during the study.

Most patients who were on oral antidiabetic medications tended to have new antidiabetic medications added, including insulin

The above categorizations attempted to create homogenous groups of patients that would facilitate comparisons across groups. However, several factors still confound the assessment of the glycemic profile within each group as well as the comparisons of glycemic profiles between these groups such as:

- Between-group differences in glycemic values at baseline
- Within-group differences in baseline anti-diabetic therapy.
- Within-group and between-group differences in the onset of antihyperglycemic intervention

For example, as shown in Figure 8-7 and Figure 8-8 baseline FPG and HbA1c levels differed between the groups, with highest baseline glucose values observed in patients who received insulin at any time during the study, and lowest in those who received no anti-diabetic medication during the study.

Patients that did not require or receive anti-diabetic treatment show a small increase in FPG within the first month of treatment followed by stabilization. No further increase in FPG was seen, despite the absence of anti-diabetic treatment after baseline.

Patients who received treatment with oral monotherapy only had a slightly larger increase in FPG than those who did not require any anti-diabetic intervention within the first month and a half of treatment and after Month 6. Greater increases in FPG levels were observed in those patients who received oral agent combinations at any time, with peak values at 0.5 month and a trend towards decrease and stabilization thereafter.

Finally, patients who initiated insulin therapy at any time during the study had the most pronounced increase in FPG levels; these peaked at Month 1 and decreased then rapidly, most likely due to the insulin therapy. FPG levels were generally stable after Month 3.

HbA1 levels increased within 2 months of treatment and remained relatively stable thereafter across all groups. The increase was smaller in patients who did not receive anti-diabetic medication and in those who received oral monotherapy only; a greater increase was seen in those receiving oral combination agents only and the greatest increase was observed in those patients receiving insulin, thereby paralleling the results seen for FPG.

In the overall population, reductions observed in FPG and HbA1c levels could be attributed to a number of factors including discontinuations, lowering of cortisol, and effective anti-diabetic medications. Careful review of individual patient profiles revealed a number of patients in whom hyperglycemia improved in response to anti-diabetic intervention (0904_00006; 0841_00007; 0107_00001; 0902_00009; 0903_00001; 0701_00007; 0706_00004). While the timing of the anti-diabetic intervention is known, the doses of anti-diabetic medications were not captured.

Figure 8-7 Mean FPG (mg/dL) from baseline to Month 12 by post-baseline anti-diabetic therapy subgroups (B2305)

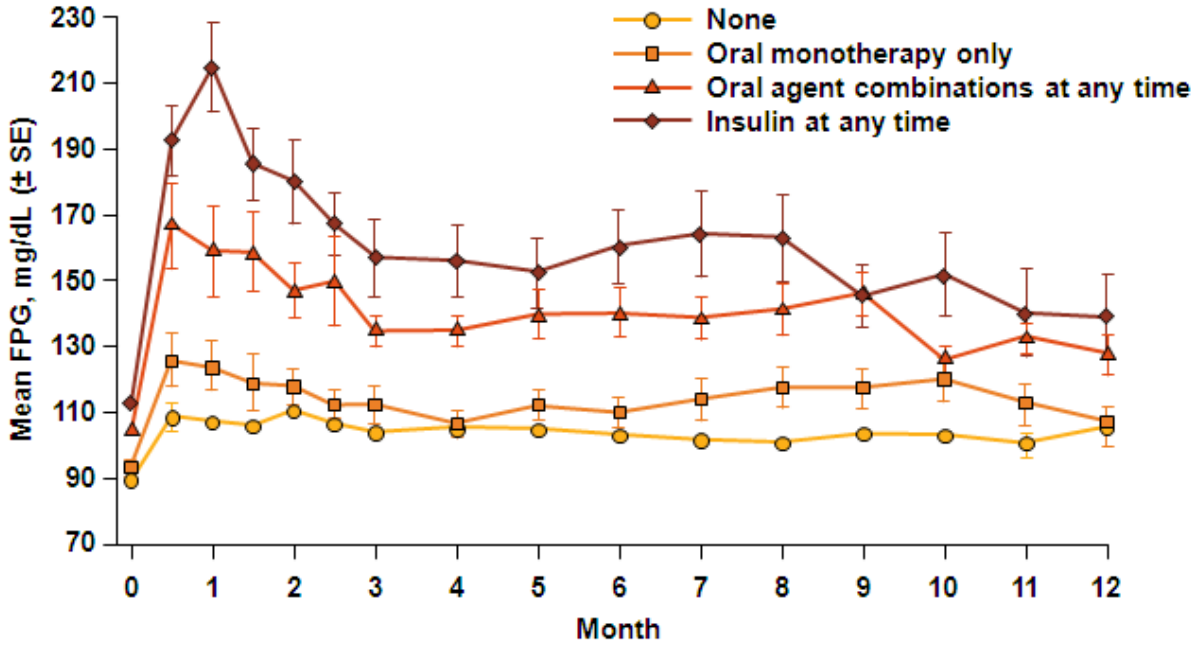
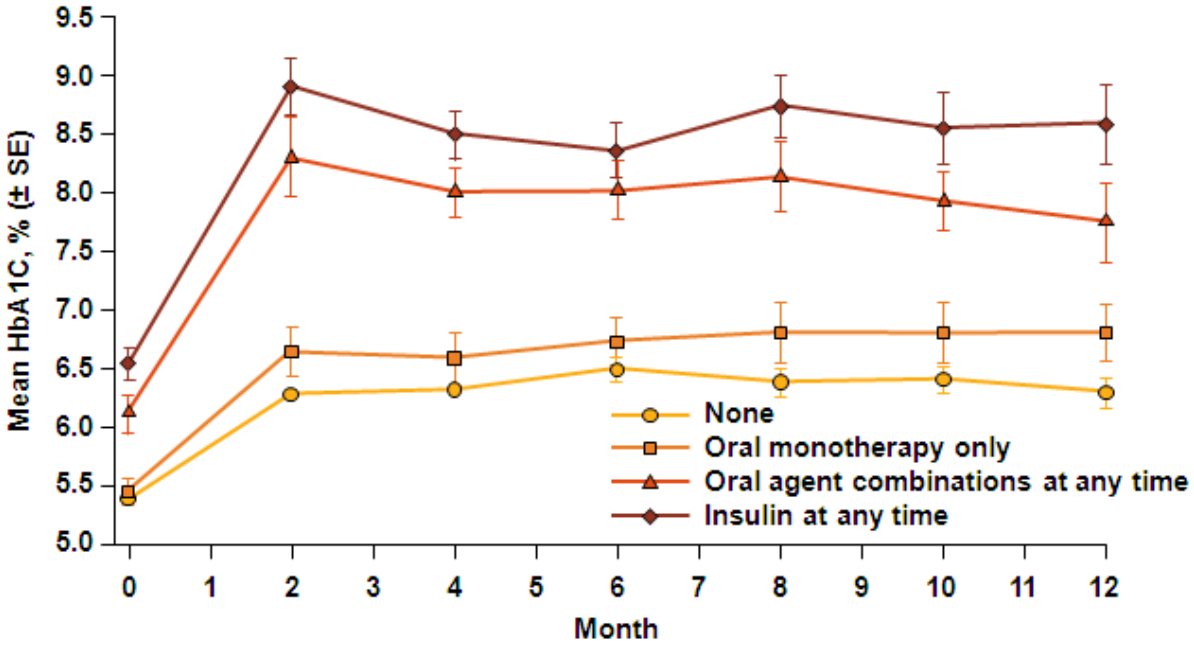


Figure 8-8 **Mean HbA1c (%) from baseline to Month 12 by post-baseline anti-diabetic therapy subgroups (B2305)**



8.3.3 PK/FPG and PK/HbA1c

Population PK/safety analysis indicated a positive correlation between glucose and pasireotide exposure in patients with Cushing's disease. Similar results were obtained with either pasireotide trough concentration or incident dose as the exposure measure. According to the models, the logarithm of FPG was linearly related to pasireotide exposure. At a given concentration or dose of pasireotide, glucose tended to be higher for patients with higher baseline glucose, with a baseline history of hyperglycemia, and for older patients. The effect of baseline hyperglycemia was less for females. The positive relationship between exposure and FPG was stronger for patients with baseline hyperglycemia but weaker for patients on antidiabetic medication. No significant effect by weight, renal function, liver function, or race on the relationship between glucose and trough concentration was observed.

A logistic regression analysis using Month 2 data (note: HbA1c was measured every 2 months, and Month 2 was before a patient's dose could be increased) showed a clear trend toward increasing probability of experiencing a $\geq$ 1% post-baseline increase of HbA1c with increasing pasireotide exposure (see Figure 13-12 in Appendix II).

8.3.4 Summary of hyperglycemia

The hyperglycemia observed in clinical studies following pasireotide therapy can be attributed to decreases in insulin secretion and incretin hormones, with no changes in insulin sensitivity. Recently available results from mechanistic studies in healthy volunteers suggest that incretin-based therapies are the most promising class of agents for the management of hyperglycemia associated with pasireotide treatment. Novartis is currently initiating a study in patients with Cushing's disease to evaluate the effect of pro-active anti-diabetic intervention on hyperglycemia associated with pasireotide treatment.

Study B2305 showed a high prevalence of alterations in glucose metabolism at baseline. Approximately 60% of patients were diabetic or pre-diabetic, and many of them were not receiving optimal treatment at baseline. AEs linked to hyperglycemia were reported in around 70% of patients overall, with a quarter of all patients reporting grade 3 events (a grade 4 event was reported in 2 patients). Hyperglycemia-related AEs were more frequent among patients who were characterized as diabetic at baseline, and less frequent among those with normal glucose tolerance at baseline. Furthermore, grade 3-4 hyperglycemia-related AEs and SAEs were most frequent among diabetic patients, and in particular those in the 900 µg b.i.d. group. Grade 3-4 hyperglycemia-related events were infrequent in patients with normal glucose tolerance at baseline, regardless of dose group.

No cases of diabetic ketoacidosis or hyperosmolar coma have been reported in B2305.

FPG levels peaked within the first month of pasireotide treatment, with higher increases seen in patients who were diabetic at baseline (in particular those randomized to 900 µg b.i.d.); thus patients' glycemic status prior to starting pasireotide therapy may serve as a meaningful predictor of future glycemic response to pasireotide. FPG levels then decrease and stabilized, most likely due to a combination of multiple factors: decreases in circulating cortisol, attenuation of effect over time, decreases in weight, decreases in insulin resistance, and anti-diabetic intervention. HbA1c levels increased and stabilized by Month 2 in both dose groups, with higher increases seen in pre-diabetic and diabetic patients. Careful review of individual patient profiles revealed a number of patients in whom hyperglycemia improved in response to anti-diabetic intervention. Pasireotide-induced hyperglycemia was rapidly reversible upon discontinuation of treatment, with FPG levels decreasing to near-baseline levels within 1 month after last administration of pasireotide.

Taken together, the results indicate that appropriate anti-hyperglycemic intervention can improve glycemic control in patients with Cushing's disease. The mechanism of pasireotide-induced hyperglycemia is now better understood than at the time the B2305 study was conducted, based on the results of the mechanistic studies B2216 and B2124. The increased understanding of the mechanism of hyperglycemia and optimal treatment modalities will help ensure that hyperglycemia can be optimally managed in patients with Cushing's disease receiving pasireotide therapy.

8.4 LFT increases

Elevations in transaminases and cholelithiasis are known adverse events of somatostatin analog therapy. Elevations in transaminases, cholelithiasis, and hepatitis have been reported both with lanreotide and with octreotide treatment.

The observation of the critical importance of altered liver function has been referred to informally as Hy's Law (Temple 2001, Reuben 2004). The FDA Guidance for Industry: Drug induced liver injury: premarketing clinical evaluation (2009) describes the following biochemical observations: "ALT or AST >3xULN, total bilirubin >2xULN and ALP <2xULN" as "Hy's Law criteria".

Hy's Law is essentially a translation of Zimmerman's observation that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury. Thus, a finding of ALT elevation (>3xULN and often much

greater), seen concurrently with bilirubin >2xULN, identifies a drug likely to cause severe drug-induced liver injury (fatal or requiring transplant) at a rate roughly 1/10 the rate of Hy's Law cases. It is critical to rule out other causes of injury (e.g. other drugs or viral hepatitis) and to rule out an obstructive basis for the elevated bilirubin, so that alkaline phosphatase (ALP) should not be substantially elevated. In addition to the biochemical criteria, the temporal pattern of Hy's law cases is described that the drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo which then leads to elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP)

Analyses of liver safety were conducted across the pasireotide development program, including more than 650 healthy volunteers, 156 patients with Cushing's disease and 200 patients in a compassionate use program. The analyses included changes in LFTs, AE reporting within the clinical studies and in the Novartis ARGUS safety database, a literature review, and Modeling and Simulation analyses. In addition, in vitro assessments of the potential effects of pasireotide on the inhibition of bilirubin metabolism/transport, and potential effects on the inhibition of bile acid transport were conducted.

Overall, 4 cases in the pasireotide development program were identified with biochemical findings consistent with Hy's Law. These cases, as well as the results of the overall hepatic safety evaluation, are discussed in the following sections.

8.4.1 Elevations in liver function tests across the pasireotide program

Overall there were relatively few patients or healthy volunteers who met the pre-specified criteria for elevations in LFT on pasireotide treatment (Table 8-14). In total 3 healthy volunteers had ALT/AST >3xULN and total bilirubin ≥ 2xULN, and are discussed in detail below.

The results were comparable for healthy volunteers and patients. All subjects identified with elevations in ALT/AST or total bilirubin had resolution of the elevation and a benign clinical course; the biochemical elevations were not associated with adverse clinical sequelae.

The 2 patients with elevations of total bilirubin ≥ 2×ULN, and 2 of the 3 patients with ALT or AST >10xULN had carcinoid disease; their higher LFT values are likely to be due to metastatic liver disease.

Table 8-14 Elevations in liver function tests (studies other than B2305)

	Healthy volunteers N=654 n (%)	Patients N=156 n (%)
ALT/AST >3xULN and total bilirubin ≥ 2xULN	3 (0.5)	0
ALT or AST >3×ULN	16 (2.4)	6 (3.8)
ALT or AST >5×ULN	3 (0.5)	4 (2.6)
ALT or AST >10×ULN	–	3 (1.9)
Total bilirubin ≥ 2×ULN	17[a] (2.6)	2 (1.3)

[a] Including 7 subjects with pre-existing liver disease and elevations of total bilirubin
Patients treated with pasireotide includes 39 patients with Cushing's disease (B2208 with extension), 72 patients with acromegaly (B2103 and B2201 with extension), and 45 patients with carcinoid syndrome (B2202)

Summary of cases compatible with Hy's law

Three healthy volunteers were identified with concomitant elevations of ALT/AST >3xULN and total bilirubin ≥ 2xULN. Two of these patients met the biochemical criteria for Hy's law, as ALP was < 2xULN (the third case did not have an ALP measured at the time of the concomitant elevations of ALT and total bilirubin). However, these cases did not present with the classic clinical picture of severe hepatocellular damage (associated with increases in transaminases) followed by loss of hepatic function (associated with increases in total bilirubin). The increases in ALT were mild (<4xULN), took place shortly after exposure (i.e. after 5 to 7 days), were asymptomatic, had no clinical sequelae and were reversible with discontinuation of pasireotide. Importantly, the temporal pattern of decreasing total bilirubin simultaneously with increasing ALT is not consistent with severe liver injury. Thus, these cases probably represent the coincidental and simultaneous occurrence of the mild, transient increase in ALT observed across the program coupled with the mild, transient increase in total bilirubin, independent of the occurrence of severe hepatotoxicity.

Taken together, these findings are not consistent with a clinical picture of severe hepatic toxicity consistent with the clinical presentation of Hy's Law.

In addition to these cases, a patient with Cushing's disease who received pasireotide within a compassionate use program developed findings consistent with Hy's law. The patient was diagnosed with obstructive jaundice, and was admitted to the hospital. The findings further on were more consistent with hepatitis than obstruction.

Further details on these cases are presented in Table 8-15. Time-profiles of LFTs for these cases are provided in Appendix III (Section 13).

Table 8-15 Summary of cases with biochemical findings compatible with Hy's law (all studies)

Patient (study)	Baseline LFT	LFT increase, day (level) ALT	TB	Outcomes
Healthy volunteers				
47-year-old male (B2124)	Normal	Day 7 (3.1xULN)	Day 7 (2.6xULN)	Asymptomatic TB normalized 8 days after last dose ALT normalized 18 days after last dose
44-year-old male (B2125)	Normal	Day 51 (3.2xULN)	Day 51 (4.0xULN)	Asymptomatic Day 55: TB was normal ALT normalized 18 days after last dose
46-year-old male (B2124)	Normal	Day 8 (3.1xULN)	Day 8 (2.3xULN)	Asymptomatic TB normalized 4 days after last dose ALT normalized 14 days after last dose
Patients				
37-year-old female (Compassionate use)	Day -22* ALT (1.8xULN)	Day 4 (2.4xULN) Day 9 (10.3xULN)	Day 4 (3.3xULN) Day 9 (3.9xULN)	Day 9: Diagnosed with obstructive jaundice; admitted to hospital (FU information: LFT more consistent with hepatitis than obstruction) Day 9: Study drug discontinued Day 14: ALT 5.8xULN; TB 1.5xULN Day 45: ALT and TB were normal

LFT=liver function test, TB=total bilirubin, ALT=alanine aminotransferase, ULN=upper limit of normal

*patients also had elevated ALP (1.3xULN)

8.4.2 Liver function tests in B2305

In study B2305, LFTs were monitored monthly for the first 12 months, and every 3 months thereafter. A small number of patients had elevations in LFTs (Table 8-16). Eight patients had elevations of ALT or AST >3×ULN, and a single patient had an elevation of ALT or AST >5×ULN.

Table 8-16 Elevations in liver function tests (B2305)

	Pasireotide 600 µg b.i.d. N=79 n (%)	Pasireotide 900 µg b.i.d. N=77 n (%)
ALT or AST >3×ULN	6 (7.6%)	2 (2.6%)
ALT or AST >5×ULN	1 (1.3%)	0
ALT or AST >10×ULN	0	0
Total bilirubin ≥ 2×ULN	0	0
Met biochemical criteria of Hy's Law	0	0

Only patients with post-baseline LFT assessment are included

Six patients discontinued treatment because of elevation in liver enzymes (2 patients with grade 2 and 4 patients with grade 3 AEs); one patient had elevations in GGT only, the remaining 5 had mainly elevations in ALT and GGT. Bilirubin was <ULN in these patients. LFT results returned to normal after discontinuation of pasireotide. No SAEs related to liver function were reported.

8.4.3 PK/LFT data

PK/safety analysis for LFT in healthy volunteers showed statistically significant evidence for both ALT and total bilirubin to increase systematically with pasireotide exposures (AUC, C_{max}, and C_{min}), although the strength and nature of the relationships varied across studies. The best models accounted for 31% to 53% of the observed variability. Predicted average values of ALT and total bilirubin ranged from normal to less than 2xULN at the highest exposures observed.

Among patients with Cushing's disease in study B2305, neither ALT nor total bilirubin had statistically significant systematic relationships with pasireotide trough concentrations; but for ALT there was statistically significant variability among patients, i.e. ALT increased with pasireotide trough concentration in some patients but decreased in other patients. Both ALT and total bilirubin average values decreased with time following initial elevations after one month of pasireotide s.c. treatment, although some patients had trends of increasing values.

8.4.4 Overall assessment of LFT increases and hepatic safety

Pasireotide therapy is associated with mild, acute elevations in transaminases that are transient in nature. The majority of healthy volunteers and patients across the pasireotide development program did not have elevations in any LFTs. Few patients had elevations that mandated intervention (e.g. stopping study medication), and there were no cases that were considered to be clinically severe (i.e. prolonged, sustained LFT elevations).

Three healthy volunteers in clinical studies and one patient with Cushing's disease in a compassionate use program had findings that met the biochemical criteria for Hy's Law. The 3 healthy volunteer cases did not present with the classic clinical picture of severe hepatocellular damage, whereas follow-up information regarding the patient with Cushing's disease were more consistent with hepatitis than obstruction.

In clinical studies conducted in patients, liver chemistry elevations were generally mild and transient, occurred within the first 3 months of therapy. In the majority of these cases the liver chemistry values returned to normal without discontinuation of pasireotide. Elevations of ALT were most common, followed by elevations in AST. A heterogeneous pattern in the elevations was also noted; some patients had isolated elevations of transaminases, some had isolated elevations of GGT or ALP, and some had a mixed pattern. Elevations in bilirubin were rare. There were no cases meeting Hy's law criteria in Phase II and Phase III clinical studies.

Review of the Novartis safety database and published literature did not reveal any additional or unexpected findings.

In summary, mild, acute elevations in liver chemistry enzymes of a transient nature were observed across the pasireotide development program. These changes appeared to be readily identified with usual LFT monitoring and required no additional therapy other than dose adjustment/interruption of pasireotide.

8.5 QT prolongation

8.5.1 Healthy volunteer studies

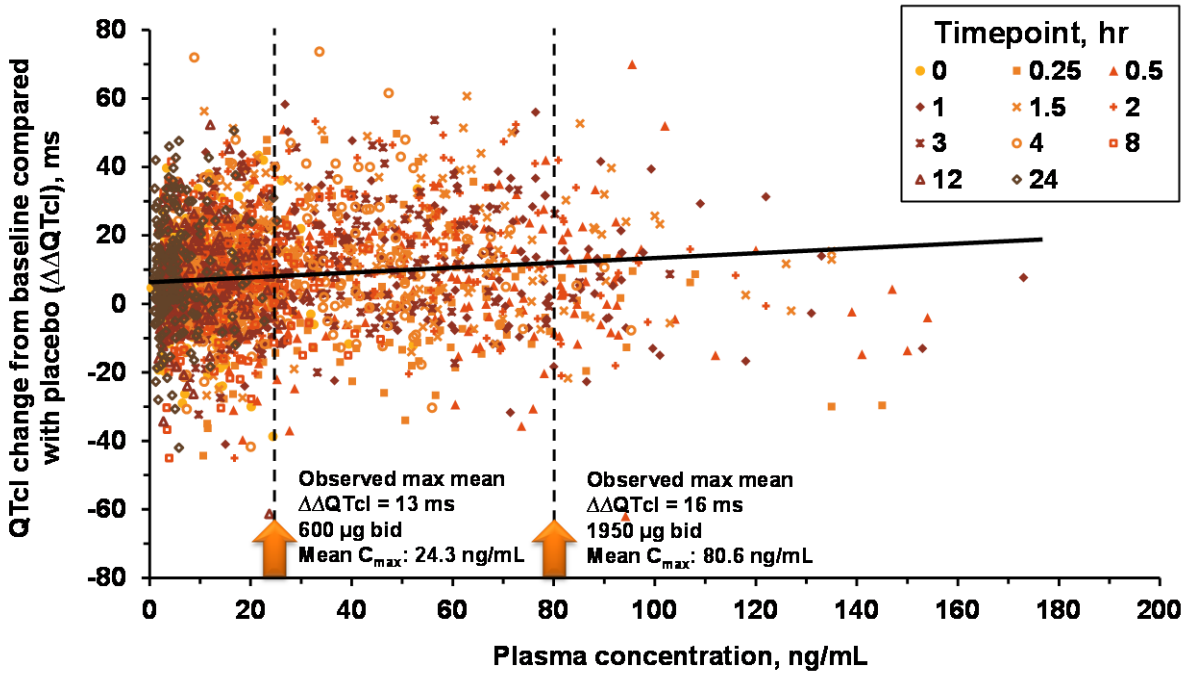
The available preclinical data suggest that pasireotide does not have the potential to delay ventricular repolarization. Two studies were conducted to evaluate the potential of pasireotide to prolong QT interval in humans. The first study (B2113) showed a transient prolongation of QTcF at the supratherapeutic dose of 1950 µg b.i.d., with a maximum placebo-subtracted change from baseline of 17.5 ms. Pasireotide treatment was also accompanied by a marked reduction in heart rate at 0 to 4 hours post-dose (a maximum change versus baseline of 10.7 bpm was observed) on day 5. There were no notable QTcF or QTcB values of more than 480 ms or more than 60 ms prolongation compared to baseline. Importantly, this study had certain limitations including the use of a single dose level and the fact that there were no time-matched pre-and-post ECGs.

A second TQT study (B2125) was undertaken to further elucidate the effect of pasireotide on QT/QTc interval. The study included two dose levels (a therapeutic dose of 600 µg b.i.d., and a supra-therapeutic dose of 1950 µg b.i.d.) of pasireotide s.c. to further evaluate a potential exposure-response effect. In addition, frequent recording of ECG and HR (via 24-hour ECG collection), in particular at low HR, were acquired as baseline data for an individual correction (QTcI) to evaluate the effect of pasireotide on QT/QTc prolongation. Finally, all pre-dose vs. post-dose comparisons were time-matched in order to minimize any intrinsic variability in cardiac function.

Results from Study B2125 are consistent with those from Study B2113 and show that pasireotide treatment is associated with QT interval prolongation and bradycardia. The maximal placebo-subtracted change from baseline in QTcI was seen at 2 hours post dose for both pasireotide doses, which was ~1.5 hours later than peak concentration of pasireotide occurred at ~0.5 hour. The mean (90% CI) difference was 13.19 ms (11.38; 15.01) for pasireotide 600 µg b.i.d., and 16.12 ms (14.30; 17.95) for pasireotide 1950 µg b.i.d.

The small difference between the 600 µg b.i.d. vs. 1950 µg b.i.d. doses in terms of effect on QTcI (i.e. 13.2 ms vs. 16.1 ms) suggests that the effect of pasireotide on QTcI is reaching a plateau in this dose range (corresponding to a concentration range of 25 to 90 ng/mL). As shown in Figure 8-9, the exposure-response effect for QTc prolongation is relatively flat between pasireotide doses 600 µg b.i.d. and 1950 µg b.i.d.

Figure 8-9 **Time-matched QTcI change from baseline from placebo versus pasireotide plasma concentration (B2125)**

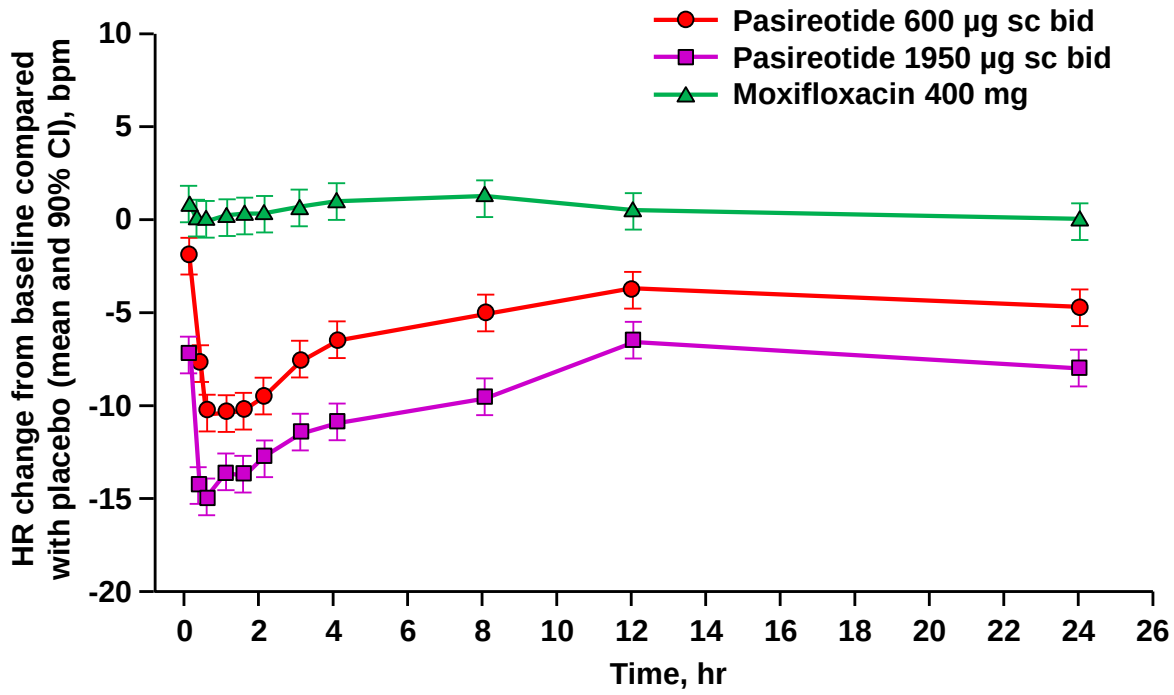


The marked bradycardic effect of pasireotide is illustrated in the plot of placebo-subtracted change from baseline for heart rate in Figure 8-10 (study B2125).

The decrease in heart rate from baseline was more pronounced with the higher pasireotide dose. The maximum placebo-subtracted change in heart rate from baseline was observed at 1 hour post dosefor pasireotide 600 µg b.i.d. (-10.39 bpm (90% CI: -11.54; -9.24)), and at 0.5 hours post dose for pasireotide 1950 µg b.i.d. (-14.91 bpm (90% CI: -16.06; -13.75)).

Relative to placebo, the effect of moxifloxacin on heart rate change was minimal.

Figure 8-10 Mean change from baseline compared to placebo for heart rate with 90% CI on day 5 (B2125)



8.5.2 QT interval analyses

Analyses across the pasireotide development program

The results of a pasireotide program-wide analysis of QTc intervals are shown in Table 8-17. The overall number of patients with newly occurring notable QTcF values (i.e. >480 ms or new QTcF >500 ms or QTcF change from baseline >60 ms) was overall low (1.3% of patients and healthy volunteers combined).

Table 8-17 Pasireotide program-wide QT/QTc interval analysis

Studies analyzed for QT/QTc values	Number of studies	Subjects with notable QTcF interval values*
All studies	16	11/829 (1.3%)
Healthy volunteers	9	3/537
Patients (Cushing's disease, acromegaly)	6	6/258
Hepatic impairment study	1	2/34**

*New QTcF >480 ms or new QTcF >500 ms or QTcF change from baseline >60 ms.

**2/19 patients with hepatic impairment; 0/15 age-, sex-, weight-matched controls.

Analyses in study B2305

As shown in Table 8-18, in B2305 there were no patients with QTcF intervals over 480 ms in the 600 µg b.i.d. group, and 3 patients with prolongation over 480 ms in the 900 µg b.i.d. group. Two patients had a QTcF prolongation >500 ms. While a third of all patients had an

increase in QTc of over 30 ms, only 2 and 3 patients, respectively, had an increase of more than 60 ms.

None of the QTcF values > 480 ms were associated with any reported AEs nor required any medical intervention or interruption of study medication, with the exception of one patient who discontinued one month after starting pasireotide 900 µg b.i.d., based on a local reading of a QTcB value of 492 ms (by central read, QTcF was 427 ms and QTcB was 466 ms). This patient had elevated QTcB at baseline (479 ms) and normal QTcF (446 ms) by local read.

Table 8-18 QTc analyses based on central read (B2305)

	Pasireotide 600 µg b.i.d. N=82			Pasireotide 900 µg b.i.d. N=80			Overall N=162		
	Total	n	%	Total	n	%	Total	N	%
QTcF									
New* > 450 ms[&]	75	3	4.0	71	4	5.6	146	7	4.8
New* > 480 ms[&]	76	0		74	3	4.1	150	3	2.0
New* > 500 ms[&]	76	0		74	2	2.7	150	2	1.3
Increase* > 30 ms[#]	77	23	29.9	74	28	37.8	151	51	33.8
Increase* > 60 ms[#]	77	2	2.6	74	3	4.1	151	5	3.3

* As compared to the prior core baseline value.
[&] Total is the number of patients with a measurement at baseline (not meeting the abnormality criteria) and a post-baseline measurement.
[#] Total is the number of patients with a measurement at both baseline and post-baseline.
n is number of patients out of Total ([&] or [#]) whose measurement met the specific threshold.

8.5.3 Adverse events indicative of arrhythmogenic potential

Analyses across the pasireotide development program

A comprehensive search for events indicative of an arrhythmogenic potential for pasireotide was conducted using the following preferred terms across the pasireotide development program using the Standardized MedDRA Query (SMQ) "Torsades de Pointes (TdP)/QT prolongation" SMQ with addition of preferred term ‘convulsion’.

The incidence of AEs was analyzed across pooled patient studies (Cushing's disease, acromegaly and carcinoid) and pooled healthy volunteer studies (Table 8-19). Note that results for B2305 are also included in the table below.

In healthy volunteers, 4 cases of syncope were reported. One of these cases was an SAE leading to study drug discontinuation in B2125. This subject developed syncope within 4 minutes of her first injection of pasireotide 1950 µg on Day 1. This event was considered to be vasovagal in nature and not related to QT prolongation. No QTcB, QTcF or QTcI outliers were recorded for this subject (Table 8-19).

In patient studies, AEs of arrhythmogenic potential were reported for a total of 17 patients (5.3%); 13 of those patients were in B2305 (see Table 8-20 below).

Table 8-19 Adverse events indicative of arrhythmogenic potential in healthy volunteers and patient studies

	Healthy volunteers N=617 n (%)	Patients N=318 n (%)
Total	4 (0.6)	17 (5.3)
Electrocardiogram QT prolonged	0	10 (3.1)
Syncope	4 (0.6)	5 (1.6)
Convulsion	0	1 (0.3)
Loss of consciousness	0	1 (0.3)

Healthy volunteers: 10 studies (B2101, B2102, B2106, B2107, B2108, B2112, B2113, B2124, B2125 and C2101 (s.c. part))

Patients: acromegaly (B2103, B2201, B2201E1), carcinoid (B2202), Cushing's disease (B2208, B2208E1, B2305)

In addition to the events described above, one patient with moderate hepatic impairment in study B2114 had a grade 1 AE of electrocardiogram QT prolonged.

Analyses in study B2305

A break-down of AEs indicative of arrhythmogenic potential is presented in (Table 8-20). Overall, the number of patients with such AEs in B2305 was low. The majority of these cases were sporadic, single occurrences of no clinical concern, however as mentioned in Section 8.5.2, one patient discontinued due to an SAE of electrocardiogram QT prolonged that was not a QTcF outlier or QTcB by central read.

Table 8-20 Adverse events indicative of arrhythmogenic potential (B2305)

Preferred term	Pasireotide 600 µg b.i.d. N=82 n (%)		Pasireotide 900 µg b.i.d. N=80 n (%)		Overall N=162
	All	Grade ¾	All	Grade 3/4	All
Total	6 (7.3)	1 (1.2)	7 (8.8)	3 (3.8)	13 (8.0)
Electrocardiogram QT prolonged	5 (6.1)	0	5 (6.3)	2 (2.5)	10 (6.2)
Syncope	1 (1.2)	1 (1.2)	2 (2.5)	1 (1.3)	3 (1.9)

A patient with multiple occurrences of an AE under one dose level is counted only once in the AE category for that dose level.

A patient with multiple AEs is counted only once in the total row.

Due to a time-delay for peak QT (~2 hours) relevant to peak pasireotide concentration (~0.5 hour), an effect compartment PK/PD model was fitted to the data from Study B2125 to characterize the hysteresis between plasma concentration and QTcI, and to enable prediction of QTcI responses to different PK profiles. The model predicted the following means and 90% CI of maximal placebo-subtracted change from baseline in QTcI:

- Cushing's disease patients, 900 µg b.i.d.: mean 14.6 ms; 90% CI: 11.8 – 17.3 ms
- Cushing's disease patients with hepatic impairment, 600 µg b.i.d.: mean: 14.3 ms; 90% CI: 11.6 – 17.0 ms

8.5.4 Overall assessment of QT prolongation

ECG assessment for patients in B2305, as well as other clinical studies conducted in the pasireotide program, revealed no evidence of cardiac safety concerns. However, after the results from the TQT study B2113 were available, a comprehensive analysis was conducted of QT/QTc interval data and the occurrence of AEs indicative of arrhythmogenic potential across all completed clinical studies of pasireotide s.c. in patients with Cushing's disease, acromegaly, carcinoid syndrome patients, subjects with hepatic impairment and healthy volunteers.

This comprehensive QT/QTc interval analysis included data from 16 Phase I-III studies involving 829 patients/subjects exposed to pasireotide s.c. Overall, the number of individuals with notable post-baseline QTcF interval values (i.e. new QTcF >480 ms or new QTcF >500 ms or QTcF change from baseline >60 ms) was low (1.3%, 11/829; patients and healthy volunteers combined).

In patients with Cushing's disease, QTcF of >500 ms was observed in 2 patients. These episodes were sporadic and mostly of single occurrence with no clinical consequence suggestive of an arrhythmogenic potential. Episodes of torsade de pointes were not observed in any of the studies.

Review of the notable outlier QT/QTc cases revealed that most cases were transitory increases in the QT and QTcF parameters which returned to normal in subsequent visits. The incidence of AEs indicative of arrhythmogenic potential across the pasireotide s.c. program was low and most cases were confounded by co-morbidities. Most of the AEs indicative of arrhythmogenic potential were of mild to moderate intensity and resolved on continued therapy with pasireotide s.c.

8.6 Hypocortisolism/Cortisol withdrawal syndrome

Hypocortisolism (and cortisol withdrawal) is an AE that is specific to patients with Cushing's disease, and is an expected effect with any successful pituitary-directed intervention. ACTH secretion from normal corticotrophs is not inhibited by somatostatin. In Cushing's disease, these corticotrophs are suppressed by elevated cortisol levels, and they do not recover immediately after cortisol levels go down. Therefore, the rapid, complete or near complete suppression of abnormal ACTH secretion from the pituitary adenoma by pasireotide may lead to a decrease in circulating levels of cortisol and potentially to transient hypocortisolism, as the normal corticotrophs need time to recover from their chronically suppressed state.

In study B2305, 13 patients (8.0%) developed hypocortisolism-related AEs. Two patients had serious events (both in the 900 µg b.i.d. groups), and one patient discontinued due to hypocortisolism. The hypocortisolism-related events presented within the first 3 months of treatment. Eight of the 13 patients with event were controlled or partially controlled in terms of UFC levels at Month 6, and all except one patient had at least one UFC $\leq$ ULN during the study, showing that pasireotide was an effective treatment in these patients.

The hypocortisolism-related events were managed successfully with a reduction in the dose of pasireotide or temporary replacement with glucocorticoids, with the exception of 2 patients.

8.7 Long-term use

Further characterization of the safety of pasireotide in Cushing's disease is provided from longer follow-up of the Phase III study B2305 and the Phase II study B2208E1 in Cushing's disease, comprising long-term safety data from 202 patients with Cushing's disease. The long-term follow-up corresponds to an additional 21 months and 30 months for study B2305 and 2208E1; respectively. The results demonstrate that pasireotide is associated with a positive benefit-risk profile in the intended target population.

The safety and tolerability profile of pasireotide observed in these updated datasets remains consistent with what was previously identified in the original NDA.

No deaths were reported in study B2305. The most frequently reported study drug related AEs with an incidence of $\geq 20\%$ were: diarrhea, nausea, hyperglycemia, cholelithiasis, abdominal pain, and diabetes mellitus. Furthermore, these AEs continue to be predominantly low grade and are generally manageable with dose adjustments/interruptions, concomitant medications, non-drug therapies, or dietary interventions. The most commonly reported grade $3 - 4$ AEs with an incidence of $\geq 5\%$ were: hyperglycemia, diabetes mellitus, and type 2 diabetes mellitus. There were no new or unexpected safety findings with a longer follow-up of 33 months.

Increased risks associated with somatostatin analogs such as hyperglycemia, gastrointestinal disturbances, cholelithiasis, QT prolongation, bradycardia, cortisol withdrawal syndrome, and abnormal liver function remained evident in B2305. However, the incidence of these AEs in the long term follow-up period was low, with none of them being severe.

Hyperglycemia-related AEs were reported in 3 additional patients during the long term follow-up period. Hyperglycemia appeared to be manageable with oral antidiabetic agents or insulin. Overall, only 3 patients discontinued the study due to hyperglycemia-related AEs during the long-term follow-up (one patient with grade 1 inadequately controlled diabetes mellitus and one patient with grade 1 hyperglycemia in the 600 µg b.i.d. group and one patient with grade 2 hypoglycemia in the 900 µg b.i.d. group).

Gastrointestinal disturbances, diarrhea and nausea-related AEs were reported in 2 additional patients each, while constipation-related AEs were reported in 3 additional patients during the long term follow-up period. Most of the cases were transient and mild in severity. Three patients discontinued the study during the long term follow-up due to gastrointestinal disturbances (2 patients with grade 1 diarrhea in the 600 µg b.i.d. group; and 1 patient with grade 1 abdominal pain, grade 1 diarrhea, and grade 1 constipation in the 900 µg b.i.d. group).

Gall bladder and biliary-related AEs were reported in 3 additional patients during the long term follow-up period. New cases of cholelithiasis were reported in 3 patients in the 600 µg b.i.d. group (2 patients with grade 2 and 1 patient with grade 3 AE). All these cases were asymptomatic and were detected during the scheduled ultrasound examinations. One patient in the 900 µg b.i.d. group discontinued the study during the long term follow-up due to grade 1 cholelithiasis.

Liver safety-related AEs were reported by 2 additional patients in the 600 µg b.i.d. group (grade 1 ALT increased and grade 1 GGT increased) during the long term follow-up period. No new cases of clinically significant elevations in transaminases and/or total bilirubin were

reported. None of the patients discontinued the study during the follow-up period due to liver safety-related AEs.

On-treatment ***QT prolongation*** (QTc > 500 ms or QTc change from baseline of > 60 ms) was not reported by any additional patients during the long term follow-up period. ECG abnormalities were a rare occurrence during the long term follow-up period, 1 additional patient experienced grade 1 QT prolongation in the 900 µg b.i.d. group and the event had resolved on the same day. None of the patients discontinued the study due to bradycardia-related AEs during the follow-up period.

Hypocortisolism- related AE was reported in 1 additional patient (grade 1 adrenocortical insufficiency acute secondary to pituitary adenoma surgery for Cushing's disease) in the 600 µg b.i.d. group during the long term follow-up. The patient withdrew consent prior to the event, which occurred two days after the last dose of study medication.

In B2208E, no new deaths, SAEs or discontinuations due to AEs occurred during the follow-up period.

Thus, the conclusion that pasireotide is associated with a manageable safety profile providing a viable long term treatment option for patients with Cushing's disease is further supported by this updated safety data.

8.8 Safety conclusions

The safety profile of pasireotide in patients with Cushing's disease is consistent with that of other somatostatin analogs, with the exception of an increased incidence of hyperglycemia. The results from B2305 and B2208 (including patients treated long-term in the extension) are consistent with the known class effects. Gastrointestinal disturbances were frequently observed, but most of the cases were transient, mild in severity and did not require additional therapy or treatment interruption. Cholelithiasis was also observed in patients with Cushing's disease, however patients were generally asymptomatic and did not require discontinuation of treatment, apart from one patient who discontinued during long-term follow-up in B2305.

Pasireotide-induced hyperglycemia was observed both in healthy volunteers and in patient studies. The hyperglycemia developed shortly after initiation of therapy, stabilized within 1-2 months, and was reversible upon discontinuation of treatment. In B2305, a third of patients with normal glucose tolerance developed diabetes mellitus. Patients with pre-existing risk for diabetes mellitus or established diabetes mellitus had a higher degree of hyperglycemia. The underlying mechanism is well understood, and is related to inhibition of insulin and incretin secretion, without changes in insulin sensitivity. Dysregulation of glucose metabolism is common in patients with Cushing's disease, and this was reflected in a high proportion of patients in B2305 who were pre-diabetic or diabetic at baseline. Patients with pre-existing risk factors for hyperglycemia are likely to have a higher degree of hyperglycemia with pasireotide treatment. Furthermore, higher pasireotide exposure is associated with a higher risk of developing hyperglycemia. There were no events of diabetic ketoacidosis or hyperosmolar coma (hyperglycemic hyperosmolar state) in study B2305.

Recent evidence from mechanistic studies and from select patients in study B2305 suggests that the hyperglycemia induced by pasireotide responds to anti-diabetic medications. Study B2124 in healthy volunteers showed that incretin-based medications (liraglutide and

vildagliptin) were most effective in ameliorating pasireotide-induced hyperglycemia. Study B2219 is being initiated to confirm this in patients with Cushing's disease.

Mild, acute elevations in transaminases were observed across the pasireotide development program. The frequency of clinically significant elevations in transaminases and/or total bilirubin was low. Elevations resolved spontaneously while on pasireotide or following treatment discontinuation and were without clinical sequelae. In B2305, 6 patients discontinued due to a hepatic AE.

Only 4 cases of concomitant elevations of ALT > 3xULN and total bilirubin ≥ 2xULN were identified in a program-wide search. However, these cases did not present with a clinical picture of severe hepatocellular damage (increases in transaminases) followed by loss of hepatic function (increases in total bilirubin) but increases of both transaminases and total bilirubin were observed simultaneously. Three of these cases occurred in healthy volunteers. In the fourth case, a patient in a compassionate use program, abnormalities in liver function were more consistent with hepatitis than obstruction. All cases resolved without clinical sequelae.

Pre-clinical data did not indicate a potential for pasireotide to prolong cardiac conduction intervals. Based on the findings of two TQT studies in healthy volunteers treated with pasireotide, a mild QT prolonging effect (maximal placebo corrected QTcI prolongation of 16.12 ms for pasireotide 1950 µg b.i.d) was found, with a relatively flat dose-response relationship between 600 µg b.i.d. and 1950 µg b.i.d. Overall, the number of healthy volunteers and patients with notable post-baseline QTcF interval values was low. In clinical studies in Cushing's patients QTcF of > 500ms was observed in 2 out of 201 patients. Overall, episodes of QT prolongation were mostly sporadic and of single occurrence with no clinical consequence suggestive of an arrhythmogenic potential. The incidence of AEs indicative of arrhythmogenic potential across the pasireotide s.c. program was low, and no episodes of torsade de pointes have been observed.

Hypocortisolism (or cortisol withdrawal) is an expected consequence of effective treatment for Cushing's disease and can be managed by appropriate dose adjustments of pasireotide or short-term exogenous glucocorticoid replacement.

Long-term follow-up data with an additional 21 months of follow-up in B2305, and 30 months for B2208E, did not reveal any new safety concerns, and showed that pasireotide was well tolerated in patients with Cushing's disease.

9 Ongoing development in Cushing's disease

Novartis is committed to the further development of pasireotide as an efficacious and safe treatment for patients with Cushing's disease, which includes a proactive hyperglycemia management study (B2219). In addition to the studies described in Table 6-1 and Table 6-2 (in Cushing's disease, acromegaly and gastroenteropancreative neuroendocrine (GEP/NET) tumors), Novartis is planning to run a study of pasireotide in combination with cabergoline (a dopamine D2 receptor agonist), to assess the efficacy and safety of this combination in Cushing's disease. The study is planned to initiate in the first quarter of 2013.

In addition, Novartis is running a compassionate use program where patients with Cushing's disease, acromegaly or NET who are not enrolled in clinical studies can benefit from treatment. Within this program, more than 300 patients have received pasireotide treatment, of which approximately 170 are patients with Cushing's disease (as of September 2012). Novartis is supplying pasireotide based on case-by-case review of requests by treating clinicians. Data collection in the context in this program is limited to SAE information; no further safety data or efficacy information is collected.

10 Risk management

10.1 Background

Pasireotide has been studied in a broad and comprehensive clinical development program. To ensure the continued assessment of the benefit-risk profile of pasireotide, proactive safety surveillance and evaluation in the postmarketing period is planned. Novartis has developed an European Risk Management Plan (RMP) to address identified and potential risks associated with pasireotide treatment. The RMP outlines risk management activities, such as labeling, educational materials, and pharmacovigilance, which will be undertaken by Novartis for these risk areas. Post-marketing safety assessments include routine pharmacovigilance and ongoing clinical studies. In addition to routine surveillance activities, targeted questionnaires are used to gather additional information on selected events reported in ongoing and future clinical studies for important safety topics, such as hyperglycemia, hypocortisolism, and QTc prolongation.

To further evaluate long-term safety and efficacy of pasireotide in patients with Cushing's disease, Novartis is initiating the Cushing's disease registry study B2410, with a planned first patient enrolled late 2012 (Table 6-2). This study is a post-approval commitment to the EMA.

Known somatostatin analog class effects

The risks that could be categorized as a class effect for somatostatin analogs are QT prolongation, bradycardia, hyperglycemia, cholelithiasis, hematological abnormalities, abnormal liver functions, injection site reactions, pancreatitis, hypothyroidism and GH/IGF-1 decrease.

Hyperglycemia is a well known class effect of somatostatin analogs and patients with Cushing's disease have a known predisposition for hyperglycemia, thus special attention is given to risk minimization activities for this adverse event. In addition, elevations in LFTs, QT prolongation, and hypercortisolism are key safety observations observed in patients with Cushing's disease. Risk minimization activities for these safety topics are described below. For other risks that are considered class effects of somatostatin analogs, routine pharmacovigilance activities are performed.

Risks seen in pre-clinical studies

Risks which were seen in pre-clinical studies and/or described only in a small number of patients are coagulation abnormalities, hypotension, hypocalcaemia, and gastrointestinal erosions/bleedings.

10.2 Monitoring of safety topics of special interest

Key safety observations in the pasireotide development program include hyperglycemia, elevations in LFTs, and QT prolongation. In addition, hypocortisolism is a risk specific to patients with Cushing's disease who receive effective, cortisol-lowering therapy. To aid health care professionals and patients, detailed guidelines are proposed for the management of these risks in clinical practice. These guidelines will be mentioned in the Full Prescribing Information (FPI) and in other educational materials provided to patients, physicians and pharmacists as described in Section 10.3.

10.2.1 Management of hyperglycemia

The glycemic status (FPG/HbA1c) should be assessed prior to starting treatment with pasireotide. FPG/HbA1c monitoring during treatment should follow established guidelines. Self-monitoring of blood glucose and/or FPG assessments should be done every week for the first two to three months and periodically thereafter, as clinically appropriate. After treatment discontinuation, glycemic monitoring (e.g. FPG or HbA1c) should be done according to clinical practice.

If hyperglycemia develops in a patient being treated with pasireotide, the initiation or adjustment of antidiabetic treatment is recommended. If uncontrolled hyperglycemia persists despite appropriate medical management, the dose of pasireotide should be reduced or pasireotide treatment discontinued.

Cushing’s disease patients with poor glycemic control (as defined by HbA1c values >8% while receiving antidiabetic therapy) may be at higher risk of developing severe hyperglycemia and associated complications. In patients with poor glycemic control, diabetes management and monitoring should be intensified prior to initiation and during pasireotide therapy.

10.2.2 Management of liver safety

Monitoring of liver chemistry is recommended prior to treatment with pasireotide, after the first 1-2 weeks on treatment, and after the first 2-3 months on treatment. Thereafter, liver chemistry should be monitored as clinically appropriate.

Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding. If the finding is confirmed, the patient should be followed with frequent liver function monitoring until values return to pre-treatment levels.

Therapy with pasireotide should be permanently discontinued if the patient develops jaundice or other signs suggestive of clinically significant liver impairment, in the event of a sustained increase in AST or ALT of 5xULN or greater, or if ALT or AST elevations greater than 3xULN occur concurrently with bilirubin elevations greater than 2xULN. Following discontinuation of treatment with pasireotide, patients should be monitored until resolution.

10.2.3 Management of cardiovascular safety

Patients with cardiac disease and/or risk factor for bradycardia, such as history of clinically significant bradycardia or acute myocardial infarction, high-grade heart block, congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia,

ventricular fibrillation, should be carefully monitored. Dose adjustments of drugs such as beta-blockers, calcium channel blockers, or agents to control electrolyte balance may be necessary.

Pasireotide should be used with caution in patients who are at significant risk of developing prolongation of QTc, such as those:

- with congenital long QT prolongation
- with uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia.
- taking anti-arrhythmic medicinal products or other substances that are known to lead to QT prolongation
- with hypokalemia and/or hypomagnesemia.

Monitoring for an effect on the QTc interval is advisable and a baseline ECG is recommended prior to initiating therapy with pasireotide and as clinically indicated. Hypokalemia or hypomagnesemia must be corrected prior to pasireotide administration and should be monitored periodically during therapy.

10.2.4 Management of hypocortisolism

It is advisable to monitor and instruct patients on the signs and symptoms associated with hypocortisolism (e.g. weakness, fatigue, anorexia, nausea, vomiting, hypotension, hyponatraemia or hypoglycemia). In case of documented hypocortisolism, temporary dose reduction or interruption of treatment with pasireotide, as well as exogenous steroid (glucocorticoid) replacement therapy may be necessary.

10.3 Medication Guide for patients

Novartis has developed a Medication Guide to be used by patients to help ensure the safe and effective use of pasireotide in patients with Cushing's disease. This material provides information on the possible adverse effects associated with pasireotide treatment, as well as what patients should communicate to their doctor prior to and while taking pasireotide. Importantly, detailed information is provided on the monitoring and management of hyperglycemia. Information on pasireotide dosing, including the possibility of different starting doses and dose increases or decreases is also provided.

Patients will receive the Medication Guide each time they receive pasireotide from the pharmacy. Additional guides will be available on the pasireotide website or by calling Novartis on a toll-free number. Physicians and pharmacists will be provided with the Medication Guide as well as the FPI and will review important information as highlighted in the Medication Guide with the patient as needed.

Distribution of pasireotide to patients

Novartis plans to distribute pasireotide through a single specialty pharmacy. Physicians can submit their prescriptions through this single specialty pharmacy to have Signifor delivered directly to the patient. This provides a mechanism for pasireotide to be made available promptly to appropriate patients together with latest Medication Guide.

11 Overview of Benefit/Risk

11.1 Summary of benefits

The efficacy results from the Phase III study B2305 and the supportive Phase II study B2208 demonstrate that patients with Cushing's disease gain significant benefit from pasireotide treatment in terms of suppressions of biochemical markers of Cushing's disease, improvement in clinical signs and physical symptoms associated with hypercortisolism, as well as improved Cushing's disease-specific HRQL.

Pasireotide treatment results in rapid and sustained suppression of UFC levels. In B2305, the proportion of patients who were controlled (i.e normalized UFC irrespective of dose increase) at Month 6 was 15.9% and 28.8% in the 600 and 900 µg b.i.d. group, respectively, whereas the proportion of patients who were either controlled or partially controlled (i.e. >50% decrease in UFC from baseline) in the respective groups was 34.1% and 41.3%; note that the lower response rate in the 600 µg b.i.d. group relative to the 900 µg b.i.d. group was in part due to a higher proportion of patient with severe hypercortisolism (i.e. UFC >5xULN) in this group. The suppression of UFC was comparable and clinically meaningful in both dose groups and sustained with longer follow-up (>2 years) in patients who remained on treatment.

In addition to decreasing UFC levels, pasireotide treatment resulted in relevant suppression of ACTH, serum and salivary cortisol levels in both dose groups, confirming that pasireotide is a pituitary-directed, centrally acting agent. Clinically relevant decrease in tumor volume was also observed in patients with measurable tumor volume at baseline.

Clinically relevant improvements in signs and symptoms of hypercortisolism were observed with pasireotide treatment in conjunction with the decrease in UFC. Changes in parameters such as BP, weight, BMI and total cholesterol were more pronounced in patients with controlled or partially controlled Month 6 UFC than in those with uncontrolled Month 6 UFC regardless of randomized dose group. The decreases in BP were of a clinically relevant magnitude in both dose groups, (mean change from baseline to Month 6 was 6.8/4.2 mmHg in the 600 µg b.i.d. group and 11.4/5.0 mmHg in the 900 µg b.i.d. group). The decrease was more pronounced with longer follow up, and was primarily observed in patients who were hypertensive at baseline. About half of all patients (regardless of randomized dose group) had less severe physical manifestations of hypercortisolism, such as facial rubor and supraclavicular and dorsal fat pads at Month 6 than at baseline. The beneficial effect of pasireotide was generally more pronounced in patients who were controlled or partially controlled at Month 6 regardless of randomized dose group, but importantly, also patients whose UFC levels were uncontrolled (i.e. less than 50% decrease in UFC from baseline) at Month 6 benefited from treatment, as their symptoms became less severe. Patients in both dose groups experienced improvement in Cushing's disease-related quality of life, as measured by the CushingQOL instrument.

Long-term follow-up data from study B2305 and B2208 showed that improvements in biochemical markers of Cushing's disease (ACTH, UFC, and serum cortisol) as well as the clinical and physical manifestations of hypercortisolism were sustained for patients who remained on study.

11.2 Summary of risks

The safety profile of pasireotide is well characterized, and the findings in the Phase III study B2305 were largely anticipated based on preclinical data and the known class effects of somatostatin analogs, with the exception of an increased incidence of hyperglycemia. The safety data from acromegaly and carcinoid syndrome patients further supports this finding, and no new safety issues were identified in these populations.

Identified risks associated with pasireotide therapy in Cushing's disease are comparable to those seen with other somatostatin analogs in other diseases, with the exception of increased incidence of hyperglycemia. Gastrointestinal disturbances were frequently observed, but most of the cases were transient, mild in severity and did not require additional therapy or treatment interruption. Cholelithiasis is another known class effect of somatostatin analogs; most patients were asymptomatic and did not require discontinuation of treatment.

Hyperglycemia is the most clinically relevant adverse event associated with pasireotide treatment. Patients with a medical history of glucose abnormalities were at higher risk of developing hyperglycemia, underscoring the importance of early identification and management. The mechanism of hyperglycemia has been well-defined in mechanistic studies, and is shown to be secondary to inhibition of insulin and incretin secretion without changes in insulin sensitivity or hepatic glucose output. Results from B2124 in healthy volunteers and from select patients in study B2305 suggests that the pasireotide-induced hyperglycemia responds to anti-diabetic medications such as incretin-based agents (liraglutide and vildagliptin), metformin and insulin. To confirm this, study B2219 is being initiated to further investigate the optimum management of hyperglycemia in patients with Cushing's disease.

As with other somatostatin analogs, pasireotide therapy is associated with mild, acute elevations in transaminases that are transient in nature and generally not associated with adverse clinical sequelae. The majority of transaminase elevations seen across the pasireotide development program returned to baseline without dose modification or discontinuation of study medication. Patients receiving pasireotide should be monitored for LFT increases; the changes in transaminase levels are readily identified with usual LFT monitoring, and require no additional therapy other than dose adjustment/interruption of pasireotide.

QT prolongation has been reported with somatostatin analogs. Results from the TQT studies B2113 and B2125 showed that pasireotide has a QT/QTc interval-prolonging effect which falls in the 'inconclusive' category of pro-arrhythmic risk (more than 5 and less than 20 ms) as per the ICH E14 guidance. A pasireotide program-wide analysis of QT/QTc intervals and events of arrhythmogenic potential revealed no new or unexpected findings that would adversely impact cardiac safety in patients. The low rate of notable QTc outliers across the clinical program is consistent with the low rate of AEs indicative of arrhythmogenic potential. Importantly, no cases of torsade de pointes have been reported during the clinical experience with pasireotide.

As with any other pituitary-directed intervention (for example surgery), signs and symptoms of hypocortisolism (or cortisol withdrawal) can occur in patients with Cushing's disease who receive effective treatment. This condition can be managed by dose adjustments of pasireotide and/or the short-term use of exogenous glucocorticoids.

11.3 Context in the treatment of Cushing's disease

Patients with Cushing's disease have high morbidity and increased mortality rates and a significantly reduced quality of life due to chronic hypercortisolism. The initial (i.e. first line) treatment of choice for Cushing's disease is transphenoidal surgery to remove the pituitary tumor. There is no consensus on treatment for patients in whom surgery failed or surgery is not feasible. For patients with recurrent or persistent disease, repeat transphenoidal surgery is is possible, but it is associated with lower efficacy than the initial surgery (Biller et al 2008). Beyond this, radiotherapy (external beam or stereotactic radiosurgery) and bilateral adrenalectomy are alternative treatment options. All 3 treatment modalities are associated with the potential for serious side effects (i.e. hypopituitarism with transphenoidal surgery and radiotherapy; primary adrenal insufficiency requiring glucocorticoid and mineralocorticoid replacement and Nelson's syndrome with bilateral adrenalectomy).

To date, long-term data in the treatment of Cushing's disease with pharmacological agents is limited. Most studies in the literature evaluating efficacy of medical therapy in Cushing's disease are small, differ in patient's characteristics, previous treatment, medication type and doses, length of follow-up and criteria used to define control. While steroidogenesis inhibitors (ketoconazole, metyrapone, mitotane), and dopamine receptor agonists (cabergoline) have been used, sustained efficacy is limited, they have no impact on the pituitary tumor, and they have significant side effects that limit therapeutic use (Biller et al 2008, Diez and Iglesias 2007). The cortisol receptor blocker mifepristone was recently approved by the FDA for the treatment of hyperglycemia in patients with Cushing's syndrome, and has been shown to significantly improve hyperglycemia and decrease patient's weight in a clinical study. However, because mifepristone increases ACTH and cortisol levels, efficacy of mifepristone can only be assessed clinically, and the cortisol excess can lead to hypokalemia and hypertension in some patients. Furthermore, chronic mifepristone use in women may result in endometrial thickening or unexpected vaginal bleeding (Fleseriu et al 2012).

In summary, despite many years of experience in the medical management of Cushing's disease, there is no consensus on the medical management of Cushing's disease and many patients cannot be controlled effectively in the longer term (Blevins et al 2009, Tritos et al 2011, Fleseriu and Petersenn 2012, Tritos and Biller 2012).

Study B2305 is the largest prospective, randomized study conducted in patients with Cushing's disease. The majority of patients had moderate to severe hypercortisolism at baseline. The data show that pasireotide targets the pituitary tumor to produce sustained biochemical control and improvements in the signs and symptoms of hypercortisolism as well as CushingQOL. Furthermore, the safety profile of pasireotide is well characterized. Adverse events can be monitored effectively and no irreversible side effect or clinical sequelae have been observed.

Pasireotide addresses the high unmet medical need for a safe and efficacious treatment in patients with persistent/recurrent Cushing's disease, and provides a viable long-term treatment option in this hard-to-treat patient population.

11.4 Recommended use

The recommended initial dose of pasireotide is 600 µg b.i.d. by s.c. injection. A dose increase to 900 µg b.i.d. may be considered based on the response to the treatment, as long as 600 µg b.i.d. is well tolerated by the patient.

In B2305, the 900 µg b.i.d. dose group met the primary efficacy endpoint (response rate 26.3%), whereas the 600 µg b.i.d. group did not (response rate 14.6%). However, in both dose groups rapid and sustained decreases in mean UFC levels were observed. It is important to note that baseline mean UFC levels were higher in the 600 µg b.i.d. group than in the 900 µg b.i.d. group (1155.9 ± 2629.78 and 781.2 ± 926.38 nmol/24h, respectively), therefore the 600 µg b.i.d. group was intrinsically less likely to meet the primary efficacy endpoint. In addition, there is substantial overlap in exposures between the two dose groups due to the high inter-subject variability in PK. Finally, analysis of exposure-UFC relationship after adjusting for baseline UFC suggests that 600 µg b.i.d. is as effective as 900 µg b.i.d. in normalizing UFC. Analysis of exposure-safety relationship revealed a clear trend of increasing probability of hyperglycemia with increasing pasireotide exposure, indicating that the risk of developing hyperglycemia is lower with 600 µg b.i.d. than 900 µg b.i.d.

Based on the above considerations, and because there is no mechanistic rationale that starting with a lower dose has any negative impact on the response to a higher dose, a starting dose of 600 µg b.i.d. (with optional dose increase to 900 µg b.i.d.) is considered to provide a better benefit-risk profile than a starting dose of 900 µg b.i.d. The dose increase from 600 to 900 µg b.i.d. is supported by the observation that mean UFC levels decreased slightly among patients who at Month 3 had a dose increase from 600 to 900 µg b.i.d., but not among those with dose increase from 900 to 1200 µg b.i.d.

For patients with moderate hepatic impairment, a starting dose of 300 µg b.i.d. is recommended with a maximum dose of 600 µg b.i.d. Patients with severe hepatic impairment should not be treated with pasireotide, given that exposure in patients with Cushing's disease is higher than in healthy volunteers, and 69 to 79% higher in subjects with severe hepatic impairment compared to normal hepatic function.

Management of suspected adverse reactions may require temporary or permanent dose reduction. Dose reduction in 300 µg decrements is suggested.

After 2 months of initiating treatment with pasireotide, patients should be evaluated for clinical benefit. Patients who experience a significant reduction in UFC levels and/or improvement in signs or symptoms of the disease should continue receiving therapy with pasireotide as long as benefit is derived.

11.5 Overall benefit/risk assessment

Patients with Cushing's disease have high morbidity and mortality rates and a significantly reduced quality of life. For patients who fail pituitary surgery, or for whom surgery is not an option, treatment options are limited.

Pasireotide is the first pituitary-targeted medical therapy to demonstrate efficacy by directly addressing the underlying mechanism of Cushing's disease (i.e. suppression of increased ACTH secretion), with associated clinically relevant decreases in cortisol levels measured in

serum, saliva and urine that are rapid, robust and sustained with longer follow-up (>2 years). Additionally, clinically relevant improvements in signs and symptoms of hypercortisolism, such as BP, weight, BMI and cholesterol levels, were observed even in patients without complete normalization of UFC, and patients experienced improvements in their Cushing's disease-related quality of life.

The safety profile of pasireotide is well characterized, and in the pivotal study was largely that anticipated based on preclinical data and the known class effects of somatostatin analogs. Hyperglycemia is the most clinically relevant adverse event associated with pasireotide treatment. Given the recent improved understanding both of the underlying mechanism of hyperglycemia and potentially effective treatment options, hyperglycemia should be manageable in the clinical setting. Furthermore, hyperglycemia associated with pasireotide is readily reversible upon discontinuation of treatment.

As with other somatostatin analogs, pasireotide therapy was associated with mild, acute elevations in transaminases that are transient in nature, generally not associated with adverse clinical sequelae, and required no additional therapy other than dose adjustment of pasireotide. Thus, pasireotide can be safely used with appropriate LFT monitoring. In addition, QT prolongation has been reported with somatostatin analogs. The available nonclinical and clinical data with pasireotide support that the QT/QTc prolonging effect associated with pasireotide does not translate into an increased pro-arrhythmic risk in clinical practice. Finally, hypocortisolism (or cortisol withdrawal) can occur in patients with Cushing's disease who receive effective treatment, but it can be managed by dose adjustments of pasireotide and/or the short-term use of exogenous glucocorticoids.

Pasireotide has a favorable benefit/risk profile in Cushing’s disease. Because UFC levels decrease within the first months of treatment in patients who respond, patients who are not likely to achieve an optimal benefit-risk outcome with pasireotide can be identified early, thereby giving the option of early discontinuation of patients not likely to derive benefit from this drug.

The proposed labeling fully characterizes both efficacy and safety to enable appropriate use of pasireotide to maximize benefit while minimizing risks to patients. In addition, the proposed Medication Guide will provide information to patients regarding the safe use of pasireotide. The data provided in this application and the full characterization of these data in the label support the use of pasireotide in the proposed indication.

12 References

Arnaldi G, Angeli A, Atkinson AB, et al (2003) Diagnosis and Complications of Cushing’s Syndrome: A Consensus Statement. J Clin Endocrinol Metab; 88:5593-5602.

Ambrosi B, Faglia G, the multicenter Pituitary Tumor study group. Lombardia region (1991) Epidemiology of pituitary tumors. In Faglia G, Beck-Pecoz P, Ambrosi, Travaglini P, Spada A (eds). Pituitary Adenomas: New trends in basic and clinical research. Elsevier Science Publishers B.V. p 159-168.

American Diabetes Association (2010) Position statement. Diagnosis and classification of diabetes mellitus. Diabetes Care; 33(Suppl 1):S62-S69.

Assie G, Bahurel H, Coste J, et al (2007) Corticotroph tumor progression after adrenalectomy in Cushing's disease: a reappraisal of Nelson's syndrome. J Clin Endocrinol Metab; 92:172–9.

Barnett P (2003) Somatostatin and somatostatin receptor physiology. Endocrine; 20: 255-264.

Batista DL, Zhang X, Geiman R, et al (2006) The effects of SOM230 on cell proliferation and adrenocorticotropin secretion in human corticotroph pituitary adenomas. J Clin Endocrinol Metab; 91(11):4482-8

Becker G, Kocher M, Kortmann RD et al (2002) radiation therapy in the multimodal treatment approach for pituitary adenoma. Strahlenther Onkol; 178:173-86.

Biller BMK, Grossman, AB, Stewart PM, et al (2008) Treatment of adrenocorticotropin-dependent Cushing's Syndrome: a consensus statement. J Clin Endocrinol Metab; 93: 2454-62.

Blevins LS, Sanai N, Kunwar S et al (2009) An approach to the management of patients with residual Cushing's disease. J Neurooncol; 94:313-19.

Bruns C, Lewis I, Briner U, et al (2002) SOM230: a novel somatostatin peptidomimetic with broad somatotropin release inhibiting factor (SRIF) receptor binding and a unique antisecretory profile. Eur J Endocrinol; 146:707-16.

Castinetti F, Morange I, Jaquet P, et al (2008) Ketoconazole revisited: a preoperative or postoperative treatment in Cushing's disease. J Endocrinol;158:91–99.

Castinetti F, Fassnacht M, Johanssen S, et al (2009) Merits and pitfalls of mifepristone in Cushing's syndrome. Eur J Endocrinol; 160:1003-10.

Chanson P and Salenave S (2010) Metabolic syndrome in Cushing's disease. Neuroendocrinology; 92(suppl 1):96-101.

Clayton RN,Raskauskiene D, Reulen RC (2011) Mortality and morbidity in Cushing's disease over 50 years in Stoke-on-Trent, UK: audit and meta-analysis of literature. J Clin Endocrinol Metab; 96:632–42.

Daly AF, Rixhon M, Adam C, et al (2006) High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. J Clin Endocrinol Metab; 91:4769-75

Davis JRE, Farrell WE, Clayton RN (2001) Pituitary Tumours. Reproduction; 121:363-371.

Dekkers OM, Biermasz NR, Pereira AM et al (2007) Mortality in patients treated for Cushing's disease is increased, compared with patients treated for nonfunctioning pituitary macroadenoma. J Clin Endocrinol Metab; 92:976–81

Diez JJ, Iglesias P (2007) Pharmacological therapy of Cushing's Syndrome: Drugs and Indications. Mini Rev Med Chem; 5:467-80.

DHHS (2009) US Department of Health and Human Services. Food and Drug Administration. Guidance for industry patient-reported outcome measures: use in medical product development to support labeling claims. December 2009. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/UCM193282.pdf.

Etgen AM, Gonzalez-Flores O, Todd BJ (2006) The role of insulin-like growth factor-1 and growth factor-associated signal transduction pathways in estradiol and progesterone facilitation of female reproductive behaviors. Front Neurodendocrinol; 27: 363-375.

Etxabe and Vazquez (1994) Morbidity and mortality in Cushing's disease: an epidemiological report. Clin. Endocrinology; 40:479-484.

de Herder WW, van der Lely AJ, Lamberts SW.(1996) Somatostatin analogue treatment of neuroendocrine tumours. Postgrad Med J; 72(849): 403-408.

Fan Y, Menon R, Cohen P, et al (2009) Liver-specific deletion of the growth hormone receptor reveals essential role of growth hormone signaling in hepatic lipid metabolism. J Biol Chem; 284: 19937-19944

Feelders RA, de Bruin C, Pereira AM, et al (2010) Pasireotide alone or with cabergoline and ketoconazole in Cushing's disease. N Engl J Med; 362(19):1846-8.

Feelders RA, Pulgar SJ, Kempel A et al (2012) Management of endocrine disease: the burden of Cushing's disease: clinical and health-related quality of life aspects. Eur J Endocrinol; 167:311-26.

Fernandez A, Karavitaki N, Wass, JAH (2012) Prevalence of pituitatry adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). Clin Endocrinol; 72:377-82.

Fleseriu M, Biller BMK, Findling JW, et al (2012) Mifepristone, a glucocorticoid receptor antagonist, produces clinical and metabolic benefits in patients with Cushing's Syndrome. J Clin Endocrinol Metab; 97: 2039–49.

Fleseriu M and Petersenn S (2012) Medical management of Cushing's disease: what is the future? Pituitary;15:330-41

Flogstad AK, Halse J, Grass P, et al (1994) A comparison of octreotide, bromocriptine, or a combination of both drugs in acromegaly. J Clin Endocrinol Metab; 79:461-65.

GodboutA, Manavela M, Danilowicz K et al (2010) Cabergoline monotherapy in the long-term treatment of Cushing's disease. Eur J Endocrinol 163:709–16

Gyr KE, Meier R (1993)] Pharmacodynamic effects of sandostatin in the gastrointestinal tract. Digestion; 54 Suppl 1: 14-19.

Hammer GD, Tyrrell JB, Lamborn KR et al (2004) Transsphenoidal microsurgery for Cushing's disease: initial outcome and long-term results. J Clin Endocrinol Metab; 89:6348-57.

Hawn MT, Cook D, Deveney C et al (2002) Quality of life after laparoscopic bilateral adrenalectomy for Cushing's disease. Surgery; 132:1064–1068.

Hofland LJ, van der Hoek J, Feelders R, et al (2005) The multi-ligand somatostatin analogue SOM230 inhibits ACTH secretion by cultured human corticotroph adenomas via somatostatin receptor type 5. Eur J Endocrinol; 152: 645-54.

Johnson MD, Woodburn CJ, Vance ML (2003) Quality of life in patients with a pituitary adenoma. Pituitary; 6:81–7.

Lauber M, Theodoropoulou M, Sievers C et al (2006) New aspects in the diagnosis and treatment of Cushing's disease. In: Arzt E, Bronstein M, Guitelman M (eds): Pituitary Today: Physiological and Clinical Aspects. Front Horm Res. Basel, Karger, 35: 169-78.

Lindholm J, Juul S, Jorgensen JOL, et al (2001) Incidence and late prognosis of Cushing's Syndrome: A population-based study. J Clin Endrocrinol Metab; 86:117-123.

Lindsay JR, Nansel T, Baid S et al (2006) Long-term impaired quality of life in Cushing's syndrome despite initial improvement after surgical remission. J Clin Endocrinol Metab; 91:447–53.

McLeod L, Pulgar S, Nelson L, et al (2011) Psychometric evaluation of the Cushing's Quality of Life Questionnaire (CushingQOL). Presented at the 18th Annual Conference of the International Society for Quality of Life Research; October 26-29, Denver, CO (abstract)

Mirza AM, Ezzat S, Axelrad AA (1997) Insulin-like growth factor binding protein-1 is elevated in patients with polycythemia vera and stimulates erythroid burst formation in vitro. Blood; 89(6):1862-1869.

Nelson LM, Forsythe A, McLeod L et al (2012) Psychometric evaluation of the Cushing's Quality of Life Questionnaire (CushingQOL). The Patient: Patient-Centered Outcomes Research (in press)

Nieman LK, Biller BM, Findling JW et al (2008) The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab; 93:1526-40.

Norman GR, Sloan JA, Wyrwich KW (2003) Interpretation of changes in health-related quality-of-life: the remarkable universality of half a standard deviation. Med Care; 41:582-92

Orth DN, Kovacs WJ, DeBold CR (1992) The adrenal cortex. In: Wilson JD, Foster DW, (eds). William's textbook of endocrinology. 8th ed. Philadelphia: Saunders, p. 489-619.

Pivonello R, De Martino MC, De Leo M, et al (2008) Cushing's Syndrome. Endocrinol Metab Clin N Am; 37:135-49.

Pivonello R, De Martino MC, Cappabianca P at al (2009) The medical treatment of Cushing's disease: Effectiveness of chronic treatment with the dopamine agnoist cabergolone in patients unsucessfully treated by surgery. J Clin Endocrinol Metab; 94:223–230.

Petersenn S, Newell-Price J, Findling JW et al (2010) Baseline characteristics and urine free cortisol (UFC) variability of 162 patients enrolled in a randomized, double-blind, Phase III study assessing the efficacy and safety of pasireotide (SOM230) in patients with Cushing's disease [poster]. Endocrine Society Scientific Session, June 2010, San Diego (CA).

Rasmussen E, Eriksson B, Oberg K, et al. (1998) Selective effects of somatostatin analogs on human drug-metabolizing enzymes. Clinical Pharmacology and Therapeutics; 64(2):150-59.

Reichlin S (1983) Somatostatin. N Eng J Med; 309:1556-63

Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (2010) Diabetes Care; 33, Suppl 1

Reuben A (2004) Hy's Law, Hepatology; 39:574-8.

Schade R, Andersohn F, Suissa S, et al (2007) Dopamine agonists and the risk of cardiac-valve regurgitation. N Engl J Med;356:29-38.

Scalera G and Tarozzi G (1998) Somatostatin administration modifies food intake, body weight, and gut motility in rat. Peptides; 19(6):991-997

Schoenherr U, Sen K, Hu M, et al (2010) A multicenter, open-label study to assess the safety and efficacy of 600 µg SOM230, administered subcutaneously, b.i.d in patients with Cushing's disease. Clinical Study Report.

Silva AP, Schoeffter P, Weckbecker G, et al (2005) Regulation of CRH-induced secretion of ACTH and corticosterone by SOM230 in rats. Eur J Endocrinol;153:R7–R10.

Schmid HA, Schoeffter P (2004) Functional activity of the multiligand analog SOM230 at human recombinant somatostatin receptor subtypes supports its usefulness in neuroendocrine tumors. Neuroendocrinology; 80(1):47-50.

Strowsky MZ, Dashkevicz MP, Parmar RM et al (2002) Somatostatin receptor subtypes 2 and 5 inhibit corticotropin-releasing hormone-stimulated adrenocorticotropin secretion from AtT-20 cells. Neuroendocrinology; 75:339-346.

Swearingen B, Biller B, Barker FG, et al (1999) Long-term mortality after transsphenoidal surgery for Cushing disease. Ann Intern Med; 130:821-24.

Taylor HC, McLean S, Monheim K (2003) Resolution of Cushing's disease followed by secondary adrenal insufficiency after anticoagulant-associated pituitary hemorrhage: report of a case and review of the literature. Endocr Pract; 9:147-51.

Temple R (2001) Hepatotoxicity Through the Years: Impact on the FDA, presented 2/12/2001, Available from: http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/ucm122149.pdf

Tritos NA and Biller BM (2012) Advances in medical therapies for Cushing's syndrome. Discov Med;13:171-9.

Tritos NA, Biller BM, Swearingen B (2011) Management of Cushing's disease. Nat Rev Endocrinol;7:279-89.

van der Hoek J, Lamberts SW, Hofland LJ (2004) The role of somatostatin analogs in Cushing's disease. Pituitary; 7:257-64.

Van Hagen PM, Krenning EP, Kwekkeboom DJ, et al (1994) Somatostatin and the immune and haematopoietic system; a review. Eur J Clin Invest; 24:91-9

Vilar L, Naves LA, Azevedo MF et al (2010) Effectiveness of cabergoline in monotherapy and combined with ketoconazole in the management of Cushing's disease. Pituitary;13:123-9.

Webb SM, Badia X, Barahona MJ, et al (2008) Evaluation of health-related quality of life in patients with Cushing's syndrome with a new questionnaire. Eur J Endocrinol;158:623-630.

Weckbecker G, Briner U, Lewis I et al. (2002) SOM230: a new somatostatin peptidomimetic with potent inhibitory effects on the growth hormone/insulin-like growth factor-I axis in rats, primates, and dogs. Endocrinol; 143:4123-4130.

Weinstock JV, Elliott D (2000) The somatostatin immunoregulatory circuit present at sites of chronic inflammation. Eur J Endocrinol; 143:S15-S19

13 Appendices

13.1 Appendix I: Statistical appendix

13.1.1 Assessing clinical signs and symptoms of Cushing's disease

The various clinical symptoms and the corresponding methods of analyses are presented in Table 13-1. Changes in clinical signs of Cushing's disease were assessed by descriptively summarizing the change in BP, BMI, waist circumference and weight from baseline to Months 3, 6 and 12 for each of the randomized dose groups. In addition, the proportions of patients satisfying the clinically relevant thresholds specified in Table 13-1 were calculated along with the 95% CIs at Months 3, 6 and 12.

These summaries were also prepared for the three efficacy analysis subsets (Controlled, Partially Controlled, and Uncontrolled) within each randomized dose group.

Table 13-1 Assessments of clinical signs and symptoms of Cushing's disease

Continuous parameters	**Unit, Scale**	**Clinically relevant threshold**
Standing systolic BP	mmHg	≤ 140 mmHg
Sitting systolic BP	mmHg, mean of 3 assessments	mean of 3 assessments ≤ 140 mmHg
Standing diastolic BP	mmHg	≤ 90 mmHg
Sitting diastolic BP	mmHg, mean of 3 assessments	mean of 3 assessments ≤ 90 mmHg
BMI	kg/m^2, Class levels: 1= <25.0, 2= 25.0 - <30.0, 3= ≥ 30.0	% of patients reducing by at least one class level
Waist circumference	cm	% of patients reducing by 5%
		% of patients reducing by 10%
Weight	Kg	% of patients reducing by 5%
Other parameters	**Scale**	**Analysis method***
Depression	0=minimum, 63=maximum Class levels: 0-13=minimal, 14-19=mild, 20-28=moderate, 29-63=severe	Beck Depression Inventory II, Counts & shifts from baseline
Facial Rubor (redness)	0=none, 1=mild, 2=moderate, 3=severe	Photographic interpretation, counts & shifts from baseline
Hirsutism	0=none, 1=mild, 2=moderate, 3=severe	Photographic interpretation
	Scoring in females only	Actual and % change from baseline
Hirsutism (Ferriman-Gallway scoring)	0=minimum, 36=maximum Scoring in females only	Photographic interpretation, Ferriman-Gallway score, actual and % change from baseline
Supraclavicular fat pads	0=none, 1=mild, 2=moderate, 3=severe	Photographic interpretation, counts & shifts from baseline
Dorsal fat pads	0=none, 1=mild, 2=moderate, 3=severe	Photographic interpretation. counts & shifts from baseline
Muscle strength	0= able to stand easily with arms extended, 1 = able to stand after several efforts without using arms as assistance, 2=able to stand only by using arms as assistance 3= completely unable to stand	Direct observation of ability to stand unaided. Counts & shifts from baseline

Bone mineral density (lumbar vertebrae, proximal femur total hip, femur neck, and total hip)	Continuous	DXA—descriptive and % change from baseline
Body composition	Continuous	DXA—descriptive and % change from baseline by dose group
Striae	0=none, 1=mild, 2=moderate, 3=severe	Photographic interpretation, counts & shifts from baseline
Bruising	0=none, 1=mild, 2=moderate, 3=severe	Photographic interpretation, count s & shifts from baseline

BP=blood pressure; BMI=body-mass index; DXA=dual-energy X-ray absorptiometry

*All photographic interpretation was performed by an independent blinded expert physician.

13.1.2 Health-related quality of life

A 12-item, disease-specific questionnaire (CushingQOL) developed by Dr. Susan Webb and Dr. Xavier Badia to assess the impact of Cushing's syndrome (CS) on health-related quality of life (Webb et al 2008). The questions and responses are shown below.

Evidence supporting use of the CushingQOL includes good content validity both in terms of the item generation approach using direct patient input from the in-depth interviews in Spain and from open-ended cognitive debriefing interviews with CS patients in five countries, and by the comprehensiveness of item content (Webb et al 2008). Specifically, the CushingQOL includes one or more items representing six of the most frequently-measured health-related QOL domains including patient-reported impact on: a) cognitive functioning, b) pain, c) psychological distress, d) role and social functioning, e) sleep adequacy, and f) worry about health.

Psychometric evaluations support the method used in estimating a single summary CushingQOL score with satisfactory reliability (Webb et al 2008); the latter favorable evaluations were replicated in the current trial (Nelson et al, in press). Empirical validity as a measure of health-related QOL is supported by substantial correlations between the CushingQOL summary score and all eight generic SF-36 Health Survey domains ranging in magnitude from 0.60 to 0.72 (Webb et al 2008). This is consistent with findings from other published studies (Hawn et al 2002, Johnson et al 2003, Lindholm et al 2001, Lindsay et al 2006), which also documented substantial health-related QOL burden for patients with Cushing’s disease.

The empirical tests of validity in relation to the clinical parameters relevant to patients with CS were reported in the study by Webb et al including significant associations with UFC and discrimination between groups with and without hypercortisolism, as hypothesized (Webb et al 2008).

Cushing's disease QOL questionnaire – questions
1. I have trouble sleeping (I wake up during the night; it takes me a long time to get to sleep, etc.)
2. I have pain that keeps me from leading a normal life
3. My wounds take a long time to heal
4. I bruise easily
5. I am more irritable, I have sudden mood swings and angry outbursts
6. I have less self-confidence, I feel more insecure
7. I'm worried about the changes in my physical appearance due to my illness
8. I feel less like going out or seeing relatives or friends
9. I have had to give up my social or leisure activities due to my illness
10. My illness affects my everyday activities such as working or studying
11. It's difficult for me to remember things
12. I'm worried about my health in the future

Cushing's disease QOL questionnaire – responses
Response options for questions 1-6 and 8-11
☐ Always
☐ Often
☐ Sometimes
☐ Rarely
☐ Never
7. I'm worried about the changes in my physical appearance due to my illness
12. I'm worried about my health in the future
☐ Very much
☐ Quite a bit
☐ Somewhat
☐ Very little
☐ Not at all

13.1.3 Responder definition for meaningful changes in CushingQOL

The definition of a responder meaningful change of 0.5 SD units in CushingQoL scores was based on both the anchor-based approach and the distribution-based method (Nelson et al, in press) recommended in the FDA's patient-reported outcome (PRO) guidance document (DHHS, 2009). The SD at baseline for the CushingQOL score was 20.2, yielding an initial estimate of a meaningful change of 10.1, which is the 0.5 SD units.

Additionally, an anchor-based approach indicated that 10.1 SD units is a conservative standard for a meaningful response change in CushingQoL scores. Using the anchor-based method, a one-category improvement in hypercortisolism severity (baseline to Month 12) observed for 51 patients was associated with a change in CushingQoL score of 13.1 in comparison with 4.4 for those who did not show improvement, a net of 8.7 units. Based on these results and other investigation (Sloan et al 2003), a change in CushingQOL of at least 10.1 (0.5 SD) was used as the criterion for the meaningful responder definition.

13.2 Appendix II: Tables and figures not included in text

13.2.1 Additional tables and graphs for the Month 12 analysis

Table 13-2 Change in UFC (nmol/24h) from baseline (B2305)

		Pasireotide 600 µg b.i.d. N=82			Pasireotide 900 µg b.i.d. N=80		
Visit		**Actual**	**Change from baseline: Actual**	**Change from baseline: Percent**	**Actual**	**Change from baseline: Actual**	**Change from baseline: Percent**
Baseline	n	77			76		
	Mean	1155.9			781.9		
	SD	2629.78			926.38		
	Median	730.0			487.0		
	Min	219.5			195.0		
	Max	22943.8			6122.8		
Month 6	n	56	52	52	55	51	51
	Mean	366.3	-463.4	-27.5	378.7	-364.9	-48.4
	SD	330.00	826.90	104.47	752.78	555.87	30.06
	Median	254.4	-368.3	-47.9	209.5	-217.8	-47.9
	Min	15.3	-3788.8	-98.1	37.8	-3600.5	-92.3
	Max	1954.0	1649.8	542.2	5511.8	41.3	12.5
	95% CI*			(-55.9, 0.9)			(-56.6, -40.2)
Month 12	n	39	37	37	38	35	35
	Mean	351.6	-572.6	-41.3	274.3	-350.7	-54.5
	SD	394.43	941.44	76.73	555.42	380.25	32.45
	Median	225.0	-379.0	-67.6	138.7	-256.0	-62.4
	Min	24.3	-4386.3	-96.5	54.3	-1619.4	-93.4
	Max	2160.5	909.8	324.0	3508.8	176.8	45.1
	95% CI*			(-66.0,-16.6)			(-65.2,-43.7)

Patients having three or more 24h UFC assessments at a visit are included.
N is the number of patients in the full analysis set.
*95% CI shown are on the mean percentage change from baseline.

Table 13-3 Change in tumor volume (cm^3) from baseline to Month 6 and Month 12

		Pasireotide 600 µg b.i.d. N=82			Pasireotide 900 µg b.i.d. N=80		
Visit		Actual	Change from baseline: Actual	Change from baseline: Percent	Actual	Change from baseline: Actual	Change from baseline: Percent
Baseline	n	82			78		
	Mean	0.89			0.20		
	SD	3.54			0.43		
	Median	0.006			0.034		
	Min	0			0		
	Max	22.83			3.00		
Month 6	n	57	52	25	54	50	28
	Mean	0.55	0.06	9.3	0.18	–0.04	–19.0
	SD	2.16	0.27	44.02	0.42	0.15	36.82
	Median	0	0	12.6	0.024	0	–28.9
	Min	0	-0.32	-83.0	0	-0.75	-100.0
	Max	14.00	1.57	89.5	2.24	0.496	57.0
	95% CI			(-8.88, 27.47)			(-33.28, -4.73)
Month 12	n	36	33	14	37	33	18
	Mean	0.47	0.44	-9.1	0.12	-0.09	-43.8
	SD	2.24	0.19	64.38	0.32	0.23	49.5
	Median	0	0	-4.2	0	0	-42.0
	Min	0	-0.09	-100.0	0	-1.15	-100.0
	Max	13.47	1.05	113.7	1.84	0.10	73.3
	95% CI			(-46.3, 28.02)			(-68.35, -19.15)

Only patients with non-zero tumor volume at baseline are included in the Change from baseline; Percent column N is the number of patients in the full analysis set.
*95% CI shown are on the mean percentage change from baseline.

Table 13-4 Mean change from baseline to Month 6 in clinical signs of Cushing's disease by UFC response at Month 6

	Pasireotide 600 µg b.i.d.				Pasireotide 900 µg b.i.d.			
	C N=13	PC N=15	UC N=54	All N=82	C N=23	PC N=10	UC N=47	All N=80
Sitting systolic blood pressure, mmHg								
Baseline								
n	13	15	54	82	23	10	47	80
Mean	134.4	128.1	132.5	132.0	130.7	138.5	136.3	135.0
SD	25.92	17.41	17.21	18.70	14.08	32.17	19.68	20.17
Mean change from baseline								
n	11	14	34	59	21	8	28	57
Mean	-12.97	-6.81	-4.78	-6.79	-13.67	-8.79	-10.45	-11.4
SD	29.83	14.86	16.87	19.35	11.4	26.01	15.73	15.92
Sitting diastolic blood pressure, mmHg								
Baseline								
n	13	15	54	82	23	10	47	80

	Pasireotide 600 µg b.i.d.				Pasireotide 900 µg b.i.d.			
	C N=13	PC N=15	UC N=54	All N=82	C N=23	PC N=10	UC N=47	All N=80
Mean	85.7	87.9	85.1	85.7	86.4	89.8	86.7	87.0
SD	15.18	13.84	12.24	12.90	9.18	21.20	11.43	12.33
Mean change from baseline								
n	11	14	34	59	21	8	28	57
Mean	-7.48	-4.79	-2.96	-4.24	-7.87	-2.42	-3.52	-4.97
SD	18.22	12.19	12.57	13.54	9.9	17.89	10.54	11.56
BMI, kg/m^2								
Baseline								
n	13	15	54	82	23	10	47	80
Mean	29.7	30.2	30.6	30.4	29.5	27.5	31.1	30.2
SD	5.36	7.75	7.25	7.01	8.26	3.17	6.98	7.07
Mean change from baseline								
n	11	14	34	59	21	8	28	57
Mean	-1.33	-1.29	-1.08	-1.18	-2.48	-1.15	-2.06	-2.09
SD	1.42	2.31	1.4	1.64	1.78	1.18	1.75	1.72
Weight, kg								
Baseline								
n	13	15	54	82	23	10	47	80
Mean	84.1	78.7	82.2	81.9	78.2	74.0	84.4	81.3
SD	21.50	17.26	24.11	22.43	22.36	11.49	20.98	20.64
Mean change from baseline								
n	11	14	34	59	21	8	28	57
Mean	-3.7	-3.3	-2.8	-3.1	-6.6	-3.1	-5.7	-5.7
SD	4.07	5.79	3.56	4.21	4.77	3.20	4.71	4.62
Waist circumference, cm								
Baseline								
n	13	15	51	79	23	10	46	79
Mean	101.2	103.1	104.0	103.3	98.8	95.8	106.3	102.8
SD	21.35	18.64	17.76	18.32	20.38	8.75	17.7	17.73
Mean change from baseline								
n	9	14	30	53	19	8	27	54
Mean	-0.67	-2.93	-1.8	-1.91	-4	-1.38	-3.48	-3.35
SD	8.47	10	7.68	8.33	5.91	3.11	5.56	5.39
Total cholesterol, mmol/L								
Baseline								
n	13	15	54	82	23	10	47	80
Mean	5.9	5.7	5.9	5.9	5.4	5.9	5.9	5.7
SD	1.25	1.20	1.35	1.29	1.18	0.96	1.48	1.35
Mean change from baseline								
n	11	14	34	59	20	8	27	55
Mean	-0.82	-0.32	-0.22	-0.36	-0.44	-0.38	-0.29	-0.36
SD	1.14	1.23	1.28	1.24	1.16	0.65	0.94	0.98
Triglycerides, mmol/L								
Baseline								

	Pasireotide 600 µg b.i.d.				Pasireotide 900 µg b.i.d.			
	C N=13	PC N=15	UC N=54	All N=82	C N=23	PC N=10	UC N=47	All N=80
n	13	15	54	82	23	10	47	80
Mean	1.8	1.8	1.8	1.8	1.6	1.6	2.1	1.9
SD	0.92	0.93	0.88	0.88	1.06	0.55	1.39	1.24
Mean change from baseline								
n	11	14	34	59	20	8	27	55
Mean	-0.05	-0.19	0.09	0	-0.12	-0.08	0.26	0.07
SD	1.01	0.81	0.95	0.92	0.61	0.41	1.29	1
Beck depression inventory (BDI-II) score								
Baseline								
n	13	15	54	82	22	10	45	77
Mean	21.5	21.5	17.6	19.0	18.0	14.6	18.6	17.9
SD	8,82	11.74	11.57	11.24	7.79	10.31	10.92	10.01
Mean change from baseline								
n	9	14	33	56	20	8	27	55
Mean	-3.78	-4.57	-4.79	-4.57	-5.4	-5.88	-5.37	-5.45
SD	13.02	9.83	8.55	9.49	7.99	7.92	9.88	8.81
Ferriman-Galway hirsutism score (females only)								
Baseline								
n	10	11	40	61	21	9	30	60
Mean	6.7	7.4	8.7	8.1	7.7	10.1	9.9	9.2
SD	4.50	6.36	6.35	6.05	8.14	8.12	7.30	7.67
Mean change from baseline								
n	9	11	24	44	19	8	20	47
Mean	0.44	-1.18	-1.25	-0.89	-3.11	-6.5	-0.05	-2.38
SD	3.13	3.4	2.49	2.88	3.65	7.5	2.61	4.7
Lumbar vertebrae (L1-L4) bone mineral density, mg/cm^3								
Baseline								
n	11	13	43	67	16	6	39	61
Mean	0.9	0.9	1.0	1.0	1.0	1.3	1.0	1.0
SD	0.12	0.09	0.17	0.16	0.13	0.53	0.17	0.23
Mean change from baseline								
n	9	12	26	47	14	4	21	39
Mean	0	0.02	-0.01	0	-0.01	0	-0.02	-0.01
SD	0.03	0.11	0.04	0.06	0.04	0.02	0.04	0.04
Proximal femur (total hip) bone mineral density, mg/cm^3								
Baseline								
n	11	13	43	67	15	6	36	57
Mean	0.8	0.9	0.9	0.9	0.9	1.0	0.9	0.9
SD	0.12	0.18	0.17	0.16	0.14	0.09	0.17	0.15
Mean change from baseline								
n	9	12	25	46	13	5	20	38
Mean	-0.01	0.01	-0.02	-0.01	-0.02	-0.01	-0.03	-0.02
SD	0.04	0.09	0.07	0.07	0.05	0.02	0.06	0.05
Body Composition: Region (% Fat)								

	Pasireotide 600 µg b.i.d.				Pasireotide 900 µg b.i.d.			
	C N=13	PC N=15	UC N=54	All N=82	C N=23	PC N=10	UC N=47	All N=80
Baseline								
n	10	11	37	58	14	4	31	49
Mean	42.4	39.7	42	41.6	40.0	37.9	41.1	40.5
SD	9.71	9.80	6.21	7.55	9.33	8.38	7.16	7.80
Mean change from baseline								
n	7	10	22	39	11	3	18	32
Mean	-2.26	0.09	-0.08	-0.43	-0.83	-0.53	-1.09	-0.95
SD	3.05	4.2	3.75	3.77	4.99	1.62	3.87	4.06

n is the number of patients in the Full analysis set who have measurements at both Month 6 and baseline.
C= controlled; PC=partially controlled; UC=uncontrolled

Figure 13-1 **Mean (+/-SE) UFC (nmol/24h) and HDL (mmol/L) up to Month 12 (B2305)**

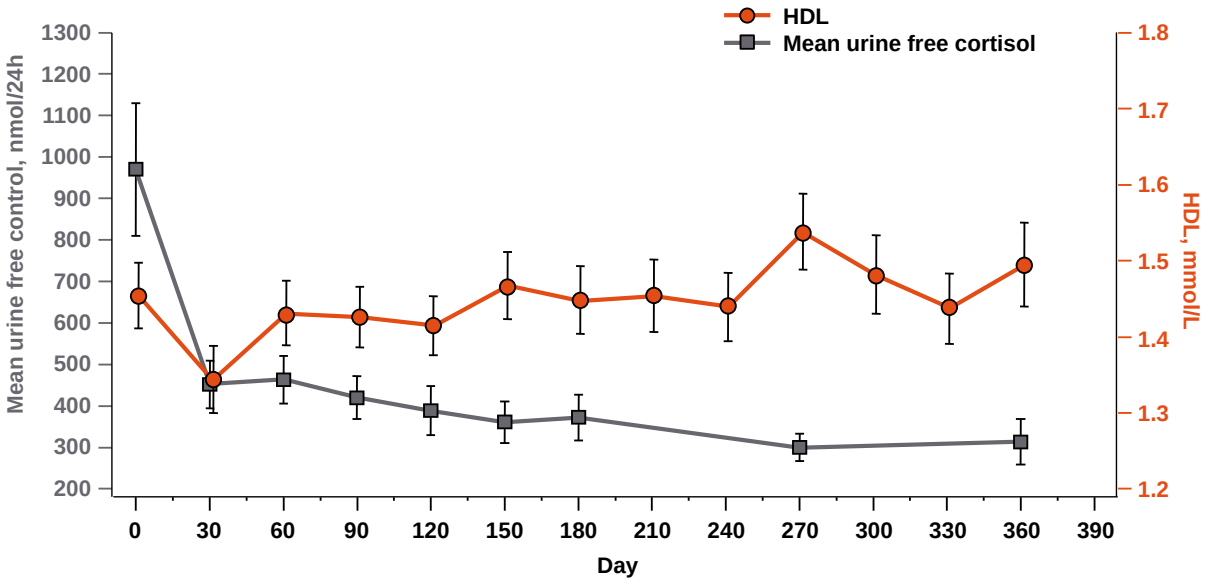


Figure 13-2 **Mean (+/-SE) UFC (nmol/24h) and LDL (mmol/L) up to Month 12 (B2305)**

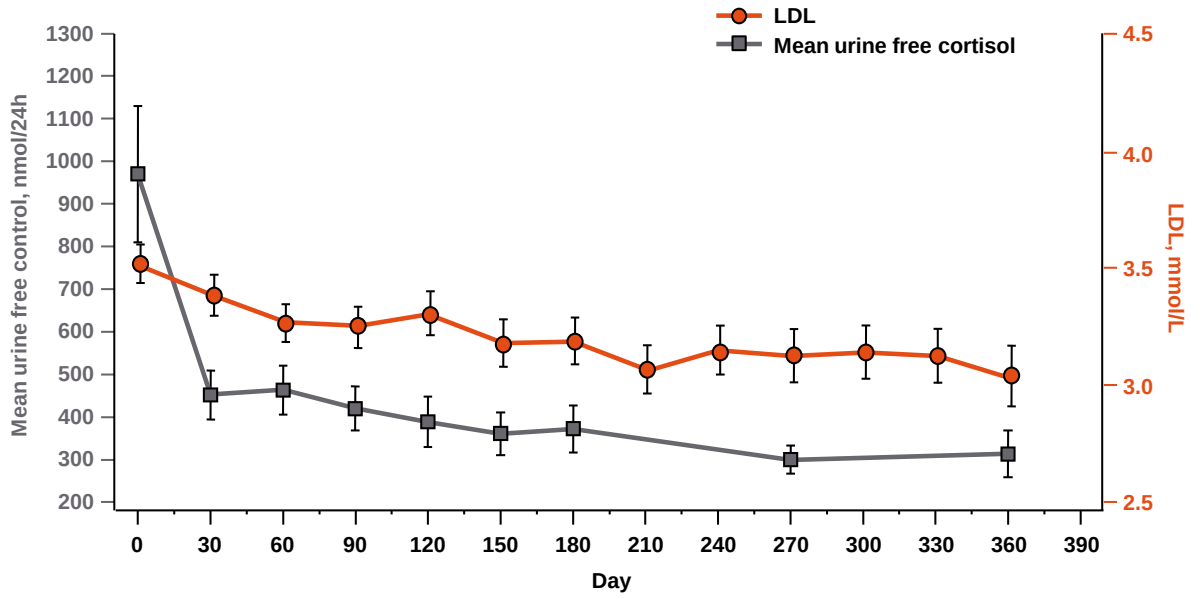
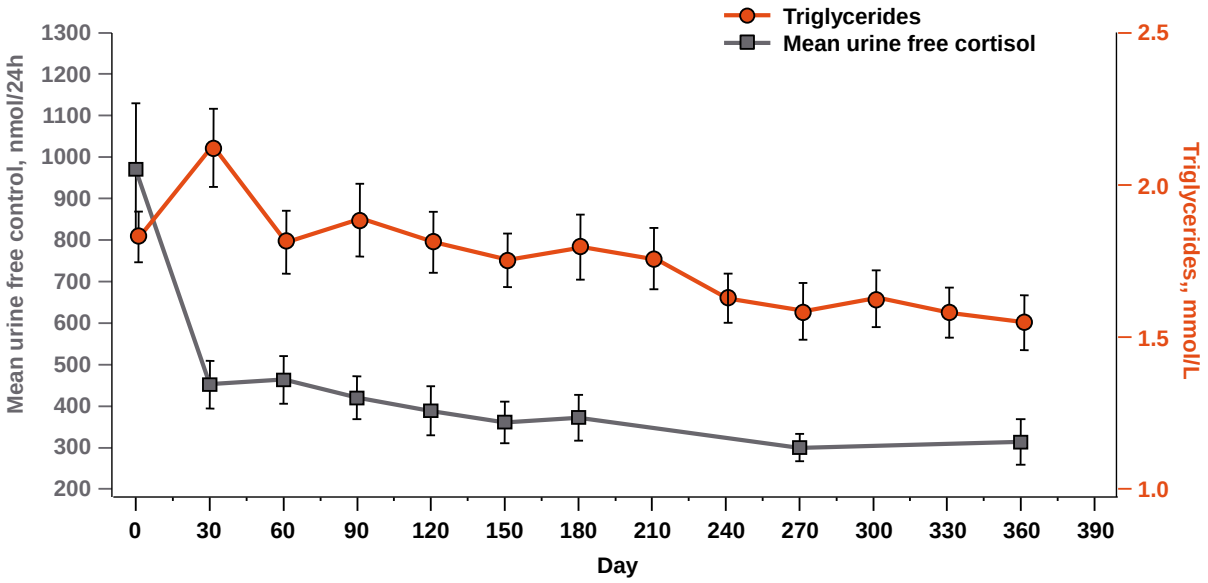


Figure 13-3 **Mean (+/-SE) UFC (nmol/24h) and triglycerides (mmol/L) up to Month 12 (B2305)**



13.2.2 Additional tables and graphs for the Month 33 analysis

Table 13-5 Patient disposition up to the Month 33 data cut-off (30-Dec-2011)

Disposition Reason	Pasireotide 600 µg b.i.d. N=83 n (%)	Pasireotide 900 µg b.i.d. N=82 n (%)	Overall N = 165 n (%)
Randomized	83 (100.0)	82 (100.0)	165 (100.0)
Randomized but not treated	1 (1.2)	2 (2.4)	3 (1.8)
Randomized and treated	**82 (98.8)**	**80 (97.6)**	**162 (98.2)**
Discontinued at any time*	59 (72.0)	62 (77.5)	121 (74.7)
Reason for discontinuation			
Adverse event(s)	17 (20.7)	18 (22.5)	35 (21.6)
Unsatisfactory therapeutic effect	23 (28.0)	27 (33.8)	50 (30.9)
Patient withdrew consent	15 (18.3)	15 (18.8)	30 (18.5)
Protocol deviation	4 (4.9)	0	4 (2.5)
Abnormal test procedure result(s)	0	1 (1.3)	1 (0.6)
Lost to follow-up	0	1 (1.3)	1 (0.6)
Discontinued at or prior to Month 6	28 (34.1)	27 (33.8)	55 (34.0)
Discontinued prior to Month 12 but after Month 6	15 (18.3)	14 (17.5)	29 (17.9)
Completed Month 12	**39 (47.6)**	**39 (48.8)**	**78 (48.1)**
Completed Month 12 and did not enter Extension phase*	13 (15.9)	7 (8.8)	20 (12.3)
Completed Month 12 and Entered Extension Phase	**26 (31.7)**	**32 (40.0)**	**58 (35.8)**
Discontinued study in Extension phase	16 (19.5)	21 (26.3)	37 (22.8)
Reason for Discontinuation in extension			
Unsatisfactory therapeutic effect	7 (8.5)	6 (7.5)	13 (8.0)
Patient withdrew consent	4 (4.9)	9 (11.3)	13 (8.0)
Adverse Event(s)	5 (6.1)	4 (5.0)	9 (5.6)
Abnormal test procedure result(s)	0	1 (1.3)	1 (0.6)
Lost to follow-up	0	1 (1.3)	1 (0.6)
Discontinued extension phase at or prior to Month 18	4 (4.9)	7 (8.8)	11 (6.8)
Discontinued prior to Month 24 but after Month 18	5 (6.1)	3 (3.8)	8 (4.9)
Discontinued at or prior to Month 30 but after Month 24	4 (4.9)	4 (5.0)	8 (4.9)
Discontinued at or prior to Month 33 but after Month 30	3 (3.7)	4 (5.0)	7 (4.3)
Ongoing in Extension phase*	**10 (12.2)**	**11 (13.8)**	**21 (13.0)**

Note: % for the first three rows based on N. % for the remaining rows based on randomized and treated subjects.
*Patients who completed Month 12 and did not enter extension phase are not counted as discontinuations.
Ongoing at the cut-off date (30-Dec-2011)

Table 13-6 UFC (nmol/24h) at selected time points up to the Month 33 data cut-off (30-Dec-2011)

	Pasireotide 600 µg b.i.d.			Pasireotide 900 µg b.i.d.		
Visit	**n**	**Mean (SD)**	**Median**	**n**	**Mean (SD)**	**Median**
Baseline	77	1155.9 (2629.78)	730.0	76	781.9 (926.38)	487.0
Month 6	56	366.3 (330.00)	254.4	55	378.7 (752.78)	209.5
Month 12	39	351.6 (394.43)	225.0	38	274.3 (555.42)	138.7
Month 18	24	193.2 (148.73)	151.8	23	157.7 (91.89)	140.0
Month 24	15	166.1 (116.22)	114.5	22	217.2 (315.08)	115.3
Month 30	12	410.2 (780.93)	83.8	18	166.3 (106.99)	173.5
Month 36*	9	258.0 (351.46)	84.0	11	783.2 (2268.69)	96.0
Month 42*	6	115.7 (80.56)	101.0	6	99.5 (43.30)	85.8
Month 48*	4	88.6 (13.41)	92.8	5	122.7 (92.13)	81.0

*Note: data is only available for those patients who had reached the Month 36, 42 or 48 time points by the time of the Month 33 data cut-off date.

13.2.3 Results from the mechanistic study B2216

Figure 13-4 Mean plasma glucagon levels during hyperglycemic clamp (B2216)

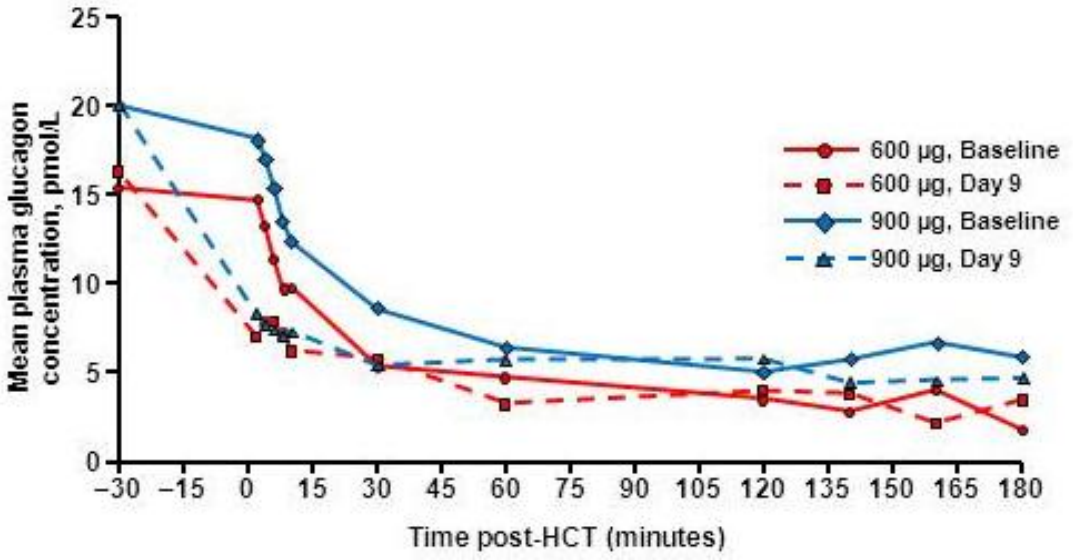
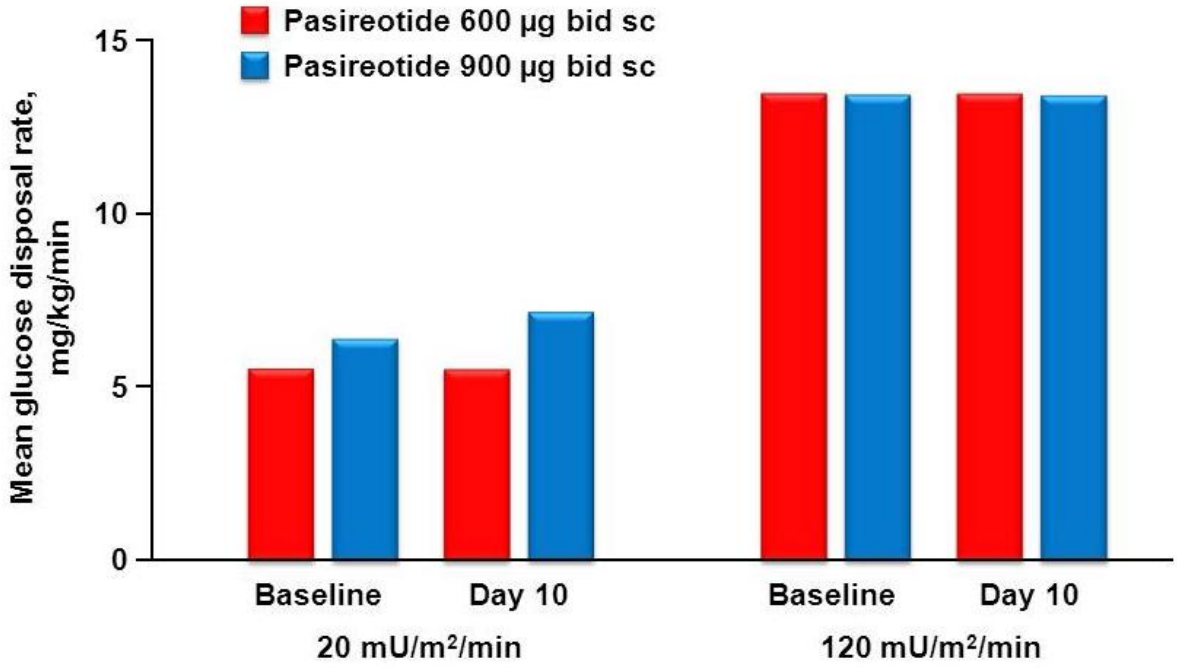


Figure 13-5 Glucose disposal rates (mg/kg/min) during hyperglycemic euglycemic clamp test (B2216)



13.3 Appendix III – LFT profiles for cases with findings compatible with Hy's Law

Three healthy volunteers in clinical studies and one patient in a compassionate use program were identified with biochemical findings compatible with Hy's law. Time-profiles of ALT, AST, ALP, GGT and total bilirubin are provided for each of these cases below.

Figure 13-6 Healthy volunteer, case no #1 (B2124)

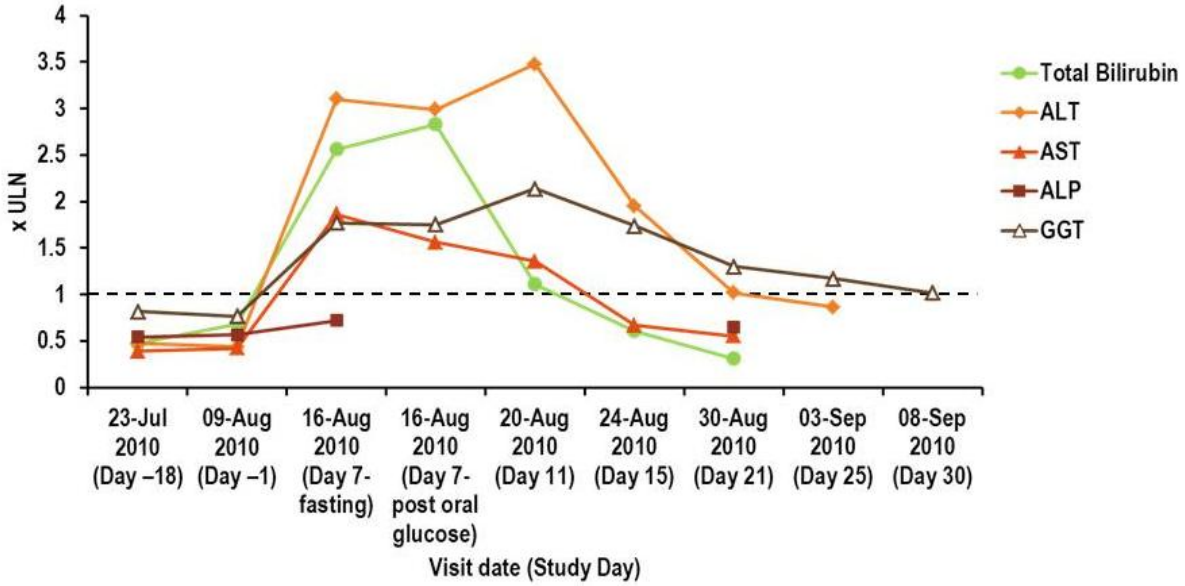
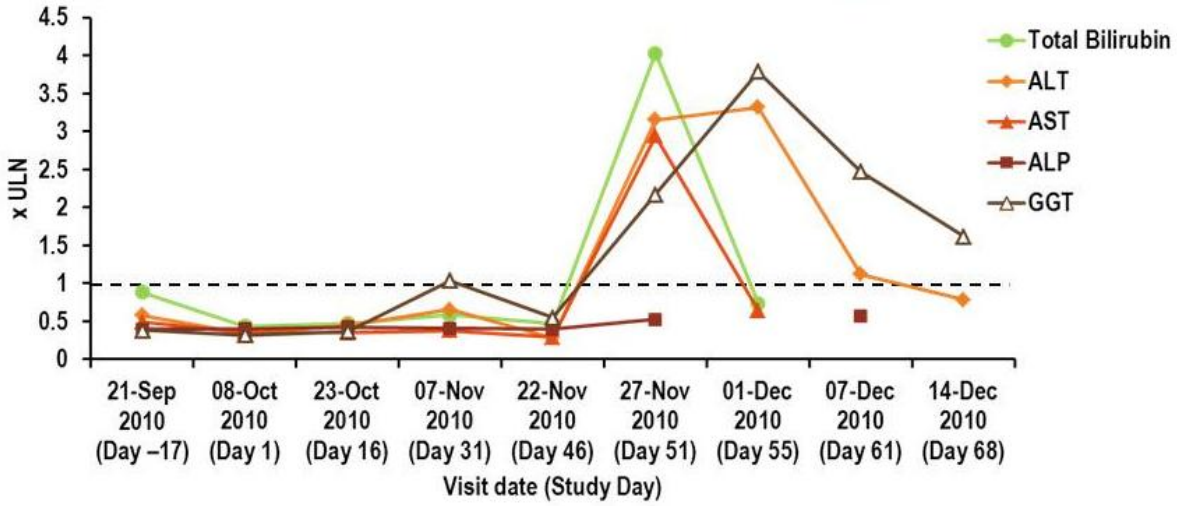
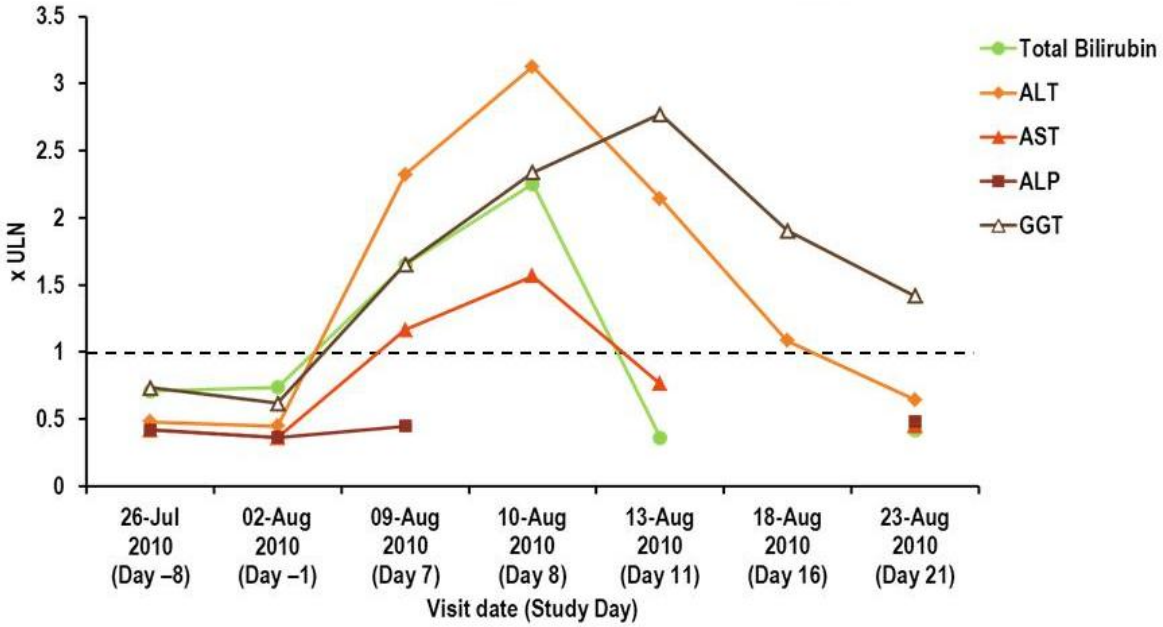


Figure 13-7 Healthy volunteer, case #2 (B2125)



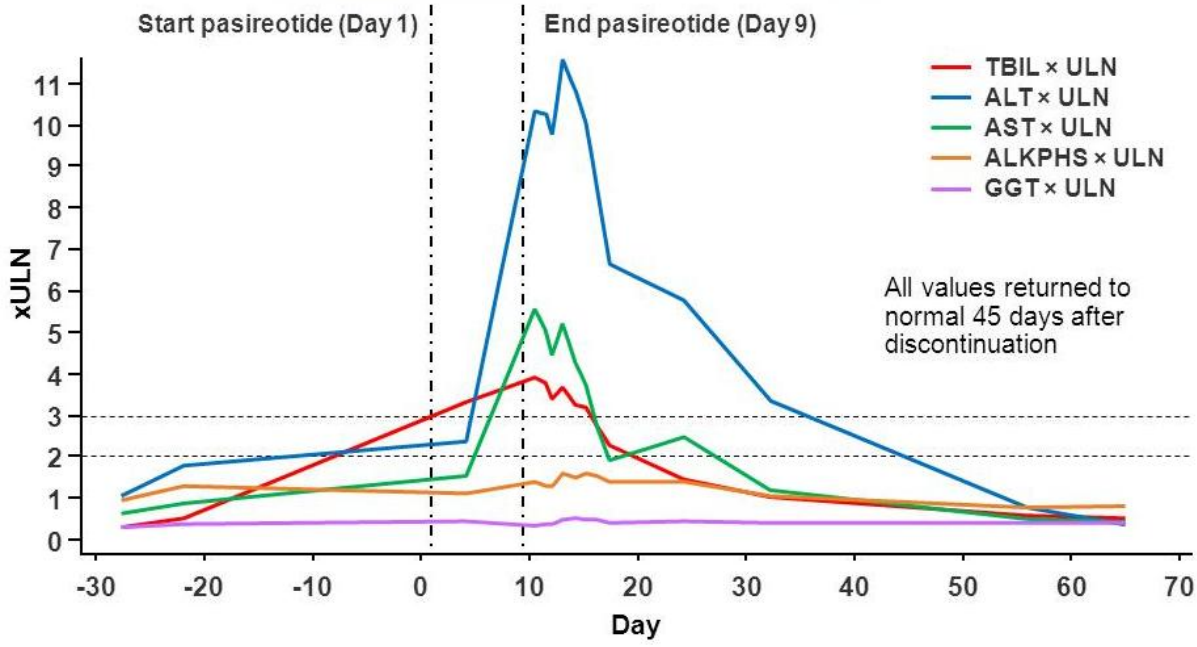
- Subject received following study medication sequences:
  - Day 1 - 5: placebo, followed by 10 day washout
  - Day 16 - 20: pasireotide 600 µg sc bid, followed by 15 day washout
  - Day 35: moxifloxacin 400 mg qd, followed by 10 day washout
  - Day 46 - 50: pasireotide 1950 µg sc bid
- Subject had extrahepatic bile duct dilatation in routine ultrasound 1 day after the last dose, which resolved 1 week later

Figure 13-8 Healthy volunteer, case #3 (B2124)



Treated with pasireotide 600 µg bid and vildagliptin 50 mg bid for 7 days.

Figure 13-9 Patient with Cushing's disease in compassionate use program



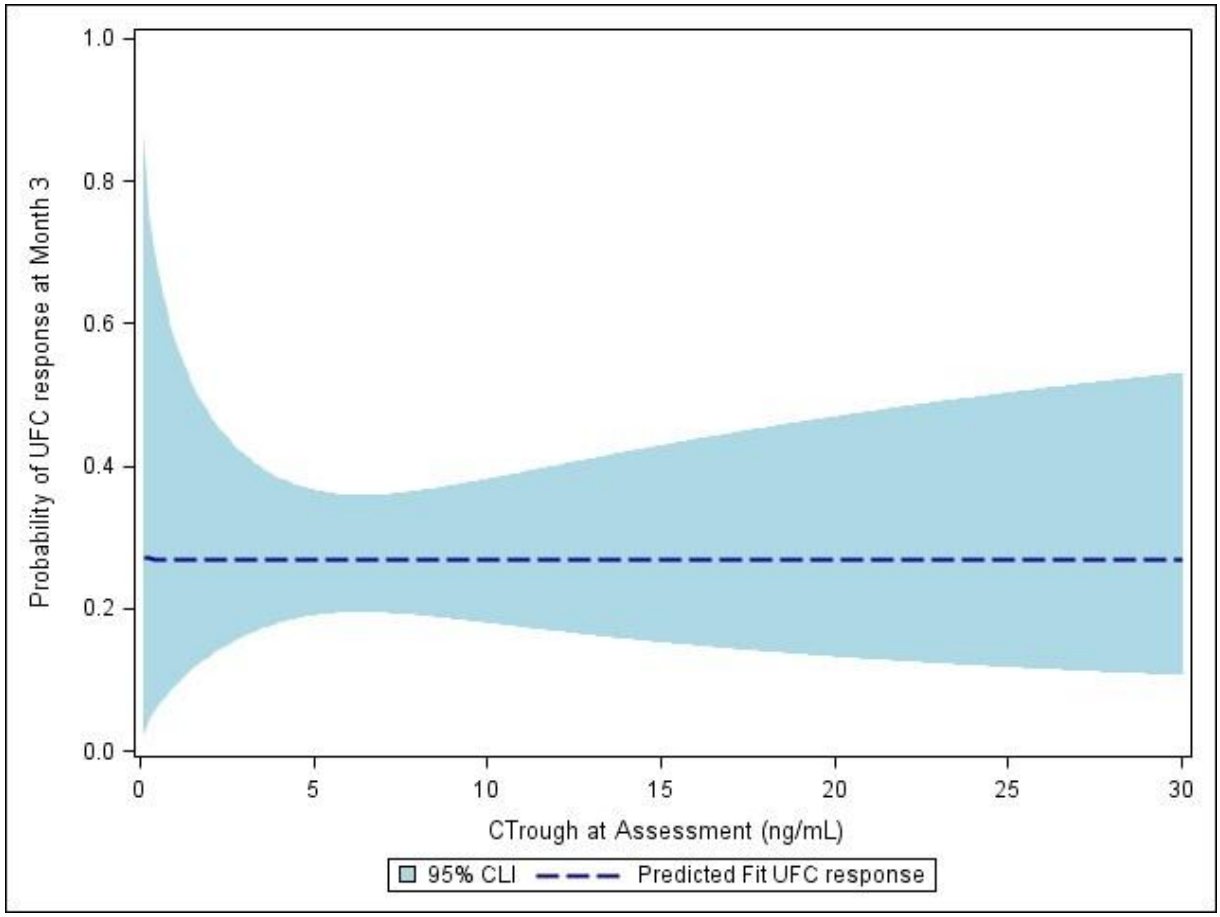
13.4 Appendix IV – analyses of exposure-response relationships relevant for dosing recommendations

The purpose of these analyses was to further explore the exposure-response relationship for efficacy (UFC normalization) and safety (hyperglycemia assessed by HbA1c).

13.4.1 Exposure-response analyses for efficacy

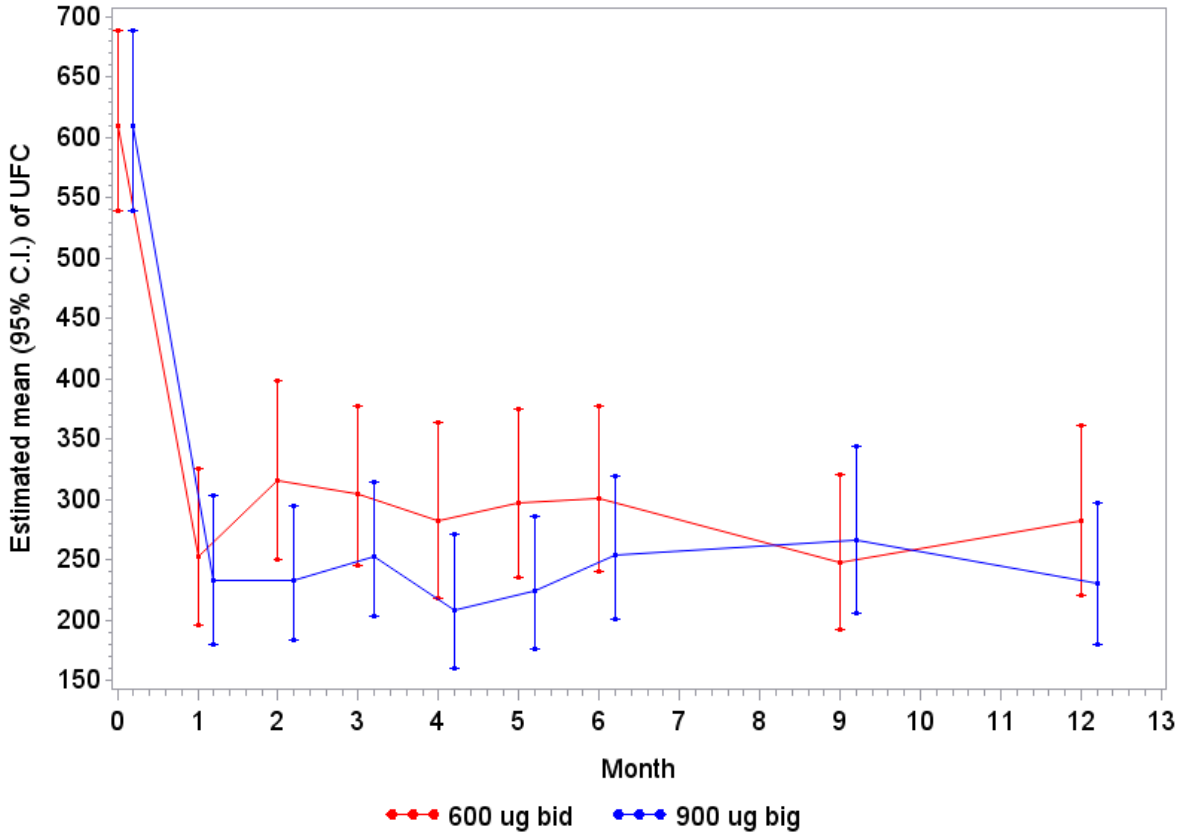
The probability of UFC normalization at Month 3 was predicted by pasireotide trough concentrations at Month 3 after adjusting for baseline UFC. As some patients underwent dose escalation after Month 3, exposure-response was explored at Month 3 instead of Month 6. There is no clear relationship between exposure (i.e. trough concentration) and probability of responding in terms of UFC normalization to pasireotide at Month 3. The predicted fit and 95% CI are plotted in Figure 13-10. These results indicate that 600 µg b.i.d. is as effective as the 900 µg b.i.d. in normalizing UFC.

Figure 13-10 Estimated probability of UFC normalization by pasireotide trough concentration at Month 3 after adjusting for baseline UFC (B2305)



A repeated measures model was used where the UFC was modeled for each dose group by averaging the baseline UFC across the two dose groups for 12 months to balance the impact of baseline UFC. The results show similar reductions in UFC in both dose groups (Figure 13-11). Note that these results are consistent with the plot of raw UFC data in Figure 7-3.

Figure 13-11 Estimated UFC levels up to Month 12 using a repeated measured model that averages baseline UFC across the two dose groups (B2305)



13.4.2 Exposure-response analysis for safety

The exposure-safety relationship was explored by analyzing the probability of developing hyperglycemia at Month 2 by pasireotide trough concentration at Month 2 after adjusting for baseline HbA1c (Figure 13-12). There is a clear trend toward increasing probability of experiencing a ≥ 1% post-baseline increase of HbA1c with increasing pasireotide exposure.

Figure 13-12 Probability of developing hyperglycemia at Month 2 by pasireotide trough concentration at Month 2 after adjusting for baseline HbA1c (B2305)